Stereospecificity of the Baeyer–Villiger Rearrangement[1]

BY KURT MISLOW AND JOSEPH BRENNER[2]

The perbenzoic acid oxidation of optically active 3-phenyl-2-butanone affords optically active phenylmethylcarbinyl acetate with the opposite sign of rotation. From the signs and magnitudes of the rotations of starting material and product it is concluded that the rearrangement implicit in that oxidation proceeds with complete retention of asymmetry and of configuration. These results are considered conclusive evidence for the intramolecular character of the reaction. Some discussion is devoted to side reactions observed to accompany preparations of the ketone.

The peracid oxidation of ketones to yield esters, a reaction involving a rearrangement whose synthetic and mechanistic aspects were first discussed by Baeyer and Villiger,[3] has been the subject of considerable investigation in recent years.[4-8] The energetics and migratory aptitudes in the rearrangement are consistent with the view that the migrating group exists as a relatively electron-deficient entity in the activated state.[4,5,9] Results of studies with dissymmetric systems[6-8] provide evidence that the rearrangement is stereospecific, so that the reaction may be considered formally analogous to the Beckmann, Wagner–Meerwein and Wolff rearrangements, inter alia.

$$C_6H_5CHCH_3COOH \xrightarrow{CH_3Li} C_6H_5CH \quad CH_3COCH_3 \xrightarrow{PBA}$$
$$\downarrow PCl_3 \quad (I)$$
$$C_6H_5CHCH_3COCl \ (II) \xrightarrow[Et_2O]{Cd(CH_3)_2} C_6H_5CHCH_3COOC_2H_5 \ (IV)$$

$$\begin{cases} C_6H_5CHCH_2OCOCH_3 \ (V) \\ C_6H_5CHCH_3COOCH_3 \ (VI) \end{cases}$$

The question of stereospecificity seemed important enough to us to warrant further investigation. The earlier work on this phase of the problem had been done exclusively with cyclic compounds, containing more than one center of asymmetry. Accordingly, and of necessity, the conclusions which were drawn regarding the stereochemistry of the oxidation were based on the isolation, generally in yields of the order of 60%, of one of a number of possible diastereomeric products. While these results appeared indicative, they did not, therefore, represent conclusive evidence for the operation of a single mechanism.

A more sensitive criterion for the stereospecificity of the reaction may be found in the rearrangement of a ketone containing a single center of asymmetry adjacent to the carbonyl function. For this purpose, 3-phenyl-2-butanone was chosen as the model compound since the phenylmethylcarbinyl group has been successfully employed as the migrating entity in the stereospecific Hofmann,[10] Curtius,[11] Beckmann,[12] Lossen,[12] Schmidt[12] and Stevens[13] rearrangements.

Product of the Oxidation.—The course of the oxidation of 3-phenyl-2-butanone (III) with perbenzoic acid (PBA) might conceivably lead to one, or a mixture, of two possible product esters, phenylmethylcarbinyl acetate (V) and methyl hydratropate (VI), depending on whether the migrating group is $C_6H_5(CH_3)CH$– or CH_3–, respectively.

A sample of pure dl-(III) was oxidized with PBA, and a comparison of the infrared spectrum of the product with the spectra of pure V and of pure VI demonstrated that the reaction led to the formation of V to the effective exclusion of VI.

Side Reactions Accompanying the Preparation of 3-Phenyl-2-butanone.—With our object the synthesis of optically active III, the choice of readily resolved hydratropic acid (I) as the starting material seemed indicated. In view of the anticipated optical lability of III, the synthetic methods available to us were severely restricted. In the main we followed the procedure previously reported,[12] which involves the reaction of cadmium dimethyl and hydratropoyl chloride (II). In an early run, a sample of hydratropic acid, $[\alpha]^{24}D$ +35.4° (c 2.99, benzene), was converted to (+)-3-phenyl-2-butanone, $\alpha^{25}D$ +19.72° (l 1, homogeneous). PBA oxidation of that ketone gave a product, $\alpha^{26}D$ +14.76° (l 1, homogeneous), which upon saponification and working up of the hydrolysis mixture yielded racemic phenylmethylcarbinol and hydratropic acid, $[\alpha]^{26}D$ +22.7° (c 1.08, benzene). Considering the fact that the oxidation of pure 3-phenyl-2-butanone had been shown to give rise exclusively to phenylmethylcarbinyl acetate, this experiment was our first indication that this method of preparation was likely to yield a product both partially racemized and accompanied by ethyl hydratropate (IV). Later runs amply buttressed this supposition. Table I summarizes some of the more significant preparations. Since the refractive indices of III and IV differ by 0.0158, a method of analysis for the mixture was available. In a test case (Table I, run no. 10) an analysis of the infrared spectrum of the product, based on the 11.58

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(2) The major portion of this paper was abstracted from the thesis submitted by Joseph Brenner to the Graduate School of New York University in partial fulfillment of the degree of Doctor of Philosophy 1952.

(3) A. Baeyer and V. Villiger, Ber., **32**, 3625 (1899); **33**, 858 (1900).

(4) S. L. Friess, THIS JOURNAL, **71**, 14, 2571 (1949); S. L. Friess and co-workers, ibid., **72**, 5518 (1950); **73**, 3968 (1951); **74**, 1302 (1952).

(5) W. E. Doering and L. Speers, ibid., **72**, 5515 (1950).

(6) W. G. Dauben and E. Hoerger, ibid., **73**, 1505 (1951).

(7) T. F. Gallagher and T. H. Kritchevsky, ibid., **72**, 882 (1950).

(8) R. B. Turner, ibid., **72**, 878 (1950).

(9) Cf. also R. Criegee, Ann., **560**, 127 (1948), and R. Robertson and W. A. Waters, J. Chem. Soc., 1574 (1948).

(10) C. L. Arcus and J. Kenyon, ibid., 916 (1939).

(11) H. I. Bernstein and F. C. Whitmore, THIS JOURNAL, **61**, 1324 (1939).

(12) A. Campbell and J. Kenyon, J. Chem. Soc., 25 (1946).

(13) A. Campbell, A. H. Houston and J. Kenyon, ibid., 93 (1947); J. H. Brewster and M. W. Kline, THIS JOURNAL, **74**, 5179 (1952).

TABLE I

| | Hydratropic acid | | | Product | | | | | 3-Phenyl-2-butanone | | |
Run no.	α^l_D (l 0.5, homog.)	t, °C.	Optical purity, %	α_D (l 0.5, homog.)	n^{25}_D	Ethyl hydratropate Wt. %	EMCR[h]	Corrected α_D (l 0.5, homog.)	Optical purity, %[k]	Racemization,[k] %
1	+43.00°	25[a]	87.1	+60.4°	1.5031	27.2	+8.7°	+71.0°	43.2	50.4
2	+43.00	25	87.1	+132.5	1.5059	9.5	+3.1	+143.1	87.1	0.0
3	+43.00	25	87.1	+96.8	1.5030	27.8	+8.9	+121.5	73.9	23.6
4	+47.56	28.3[b]	98.1	+133.9	1.5051	14.5	+5.2	+151.0	91.8	6.4
5	+47.56	28.3	98.1	+113.8	1.5047	17.2	+6.2	+130.0	79.1	19.4
6	-23.09	29	47.8	-50.35	1.5067	4.5[i]	-0.8	-52.0	(31.6)	33.8
7	-22.08	23.2[c]	45.9	-16[f]	1.5047	17.2	-2.9	-15.7	9.5	79.3
8	-22.08	23.2	45.9	-3.6	1.5072	1.3	-0.2	-3.8	2.3	95.0
9			33.3[d]	-29.3[g]	1.5044	19.0	-2.3 ·	-33.3	20.2	39.4
10			34.4[e]	+52.0	1.5070	2.5[j]	+0.3	+53.1	32.3	6.0
11	-25.05	25	40.6	-5.4	1.5074	0.0	0.0	-5.4	3.3	91.9

[a] $[\alpha]^{25}D$ +64.8° (c 2.96, chloroform). [b] $[\alpha]^{25}D$ +91.2° (c 1.05, benzene). [c] $[\alpha]^{24}D$ -42.0° (c 3.04, benzene). [d] $[\alpha]^{24}D$ -30.8° (c 3.14, benzene). [e] By dilution of 87.1% optically pure acid with inactive acid by weight. [f] Rotation decreased to -8° on standing overnight. [g] Rotation decreased to -26.7° after six weeks. [h] Estimated maximum contributing rotation, α_D (l 0.5, homog.). [i] A strong band at 11.4μ (>C=CH₂ ?), as well as at 2.8 μ (-OH), precluded an analysis of the infrared spectrum. [j] 2% from an analysis of the infrared spectrum. [k] On the assumption that no racemization occurred in run no. 2.

μ band of the contaminant (IV) (Table IV), gave a result (2% of IV) in close agreement with the estimate (2.5% of IV) which was made on the basis of the refractive index method. Thus the extent of the contamination could be gauged accurately with some confidence.[14]

The rotation of the ester IV in the mixture was not known; in order to calculate the rotation of the ketone III in the mixture, the assumption was made that the rotation of IV had its maximum value in each case, as judged by the optical purity of the starting acid I. The correction thus applied yielded the minimum rotation of the ketone. Comparison of this value with the optical purity of the starting acid I provided the information that in

(14) The presence of ethyl hydratropate can be accounted for by assuming ether cleavage under the conditions of the ketonization reaction (e.g., cf. J. Cason, Chem. Revs., 40, 15 (1947)); the cadmium or magnesium halide present in the reaction mixture may serve as the appropriate catalyst, functioning as do zinc chloride (H. W. Underwood and R. R. Wakeman, THIS JOURNAL, 52, 387 (1930)), magnesium chloride (F. C. Whitmore and W. R. Wheeler, ibid., 60, 2899 (1938)) or stannic chloride (R. L. Burwell, Jr., L. M. Elkin and L. G. Maury, ibid., 73, 2428 (1951)) under similar circumstances. Very possibly, the acid chloride, the Lewis acid and the ether may participate in a cyclic transition state complex I or II which bears a certain resemblance
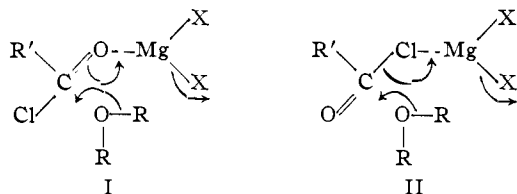
to that proposed for some formally related reactions (C. G. Swain and H. B. Boyles, ibid., 73, 870 (1951); H. S. Mosher and E. LaCombe, ibid., 72, 3994, 4991 (1950); W. E. Doering and T. C. Aschner, ibid., 71, 838 (1949), W. E. Doering and R. W. Young, ibid., 72, 631 (1950)). The reported inversion at the α-carbon atom (R. L. Burwell, et al., ref. 14) becomes a necessary consequence of this mechanism. In this connection, we suggest that the thermal decomposition of ester–Lewis acid complexes into alkyl halides (e.g., F. W. Chapman, W. S. Hummers, S. Y. Tyree and S. Yolles, ibid., 74, 5277 (1952)), which is accompanied by inversion of configuration (J. W. C. Crawford and D. Plant, J. Chem. Soc., 4492 (1952)), proceeds via a similar transition state complex (III).
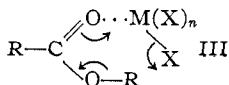
almost all runs appreciable racemization had occurred. The additional working hypothesis was made that the run in which the least racemization had occurred (run no. 2) could be used to calculate the maximum rotation of the ketone. In the light of our later results, this assumption was fully vindicated. Nevertheless, it must be stated that the result of this run was singular and fortuitous: in all other experiments the product was partially or totally racemized. In consideration of the aforesaid, it becomes less surprising to note the discrepancy between the maximum rotation of III, α_D 164.5° (l 0.5, homogeneous), calculated in this work and that previously reported,[12,15] α_D 58.1° (l 0.5, homogeneous).

A further complication was introduced by the fact, apparently here observed for the first time, that samples of acid I, prepared by the methylation and subsequent hydrolysis of benzyl cyanide,[12] were contaminated by α-phenylisobutyric acid,[16a] as detected by the isolation of α-phenylisobutyramide in the process of working up the product of the ketonization. Evidently α-phenylisobutyroyl chloride, once formed, reacts only sluggishly, if at all.[16b] In the case of resolved acid I, this contaminant always concentrated in the mother liquors ((-) fraction). The preparative method involving the oxidation of hydratropaldehyde was for these reasons much to be preferred.

In the alternate method of preparation of III, by the reaction of I with methyllithium, up to

(15) The possibility of a typographical error in the original publication must be dismissed (private communication from Dr. Joseph Kenyon).

(16) (a) The formation of this compound may be rationalized in terms of an equilibrium between benzyl cyanide carbanion and hydratroponitrile in the alkylation mixture giving rise to hydratroponitrile

$$[C_6H_5\ddot{C}HCN]^{\ominus} + C_6H_5\text{—}\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\text{—}CN \rightleftarrows$$

$$C_6H_5CH_2CN + [C_6H_5\text{—}\overset{}{\underset{\underset{\displaystyle CH_3}{|}}{\ddot{C}}}\text{—}CN]^{\ominus}$$
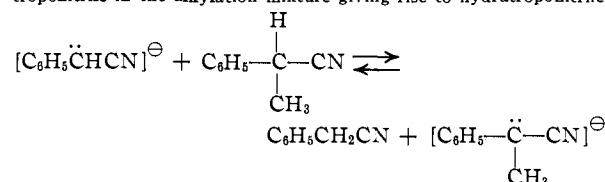
carbanion, which is capable of being further methylated. (b) In this connection, see N. H. Cromwell and H. H. Eby, THIS JOURNAL, 74, 4201 (1952).

TABLE II

	Hydratropic acid $\alpha^t{}_D$ (l 0.5, homog.)	t, °C.	Optical purity, %	Product α_D (l 0.5, homog.)	$n^{25}{}_D$	3-Phenyl-2-butanone α_D (l 0.5, homog.)	$n^{25}{}_D$	Optical purity, %	Racemization, %
Run No.									
12	+43.50°	28^a	89.8	+102.7°	1.5087	+133.16°	1.5072	81.2	9.7
13			10.6^b	+10.41	1.5082	+ 5.61	1.5076	3.41	67.8
14			44.8^c	− 45.3	1.5074	− 45.3	1.5074	27.5	38.6
15	−10.48	27	21.6	− 6.54	1.5117	− 18.01	1.5071	11.0	49.1
16	+11.17	28	23.0	+ 20.96	1.5084	+ 11.04	1.5072	6.72	70.8

^{a} $[\alpha]^{27}{}_D$ +82.5° (c 2.23, benzene). ^{b} $[\alpha]^{31}{}_D$ +9.8° (c 5.49, benzene). ^{c} $[\alpha]^{28}{}_D$ −41.5° (c 5.68, benzene).

TABLE III

	Product α_D (l 0.5, homog.)	Ethyl hydratropate Wt. %	EMCR^d	Phenylmethylcarbinyl acetate Corrected α_D (l 0.5, homog.)	Optical purity, %	Retention of asymmetry, %^{e}	Phenylmethylcarbinol $[\alpha]^{27}{}_D$ (homog.)	Optical purity, %	Retention of asymmetry, %^{e}
Run no.^{a}									
5	−35.32°	17.0^b	+6.2°	−50.0°	78.2	98.9	−34.1°	78.4	99.2
6	+19.21	4.0^b	−0.8	+20.9	32.7	(103.4)			
10	−19.75	2.0^c	+0.3	−20.5	32.1	99.5	−14.1°	32.4	100.2
17	− 3.47	...	....	− 3.47	5.43	98.5			

^{a} Run numbers refer to starting ketones listed by the same numbers in Tables I and II, with the exception of no. 17, the starting material for which, provided by combining the ketone samples obtained from runs 13 and 16, had α_D +9.06° (l 0.5, homog.), 5.51% opt. purity. ^{b} From an analysis of the infrared spectrum; $cf.$ also footnote i, Table I. ^{c} Estimated by assuming that the extent of contamination by ethyl hydratropate remained unchanged in going from ketone to oxidation product. ^{d} Estimated maximum contributing rotation, α_D (l 0.5, homog.). ^{e} Based on the optical purity of the starting ketone.

91% yields were obtained, but the product was occasionally contaminated by what appeared to be 2-methyl-3-phenyl-2-butanol.[17] The reaction was invariably accompanied by some racemization. However, either by fractionation of the product or by steam distillation of the semicarbazone in the presence of phthalic anhydride, it was eventually possible to obtain chemically pure albeit considerably racemized 3-phenyl-2-butanone (Table II).

Retention of Asymmetry in the Rearrangement. —The optical purity of the starting ketone III being known (Tables I and II), there remained the problem of determining that of the product of oxidation, V. In the case in which III was chemically pure, the problem resolved itself simply to a comparison of the rotation of V with the maximum rotation of phenylmethylcarbinyl acetate, $[\alpha]_D$ 126.1° (homogeneous). On the other hand, in several instances the starting material was contaminated by ethyl hydratropate (IV), which was carried through to the product stage. Since the refractive indices of the two esters, IV and V, differ by only 0.0013, the composition of the mixture was established by analysis of the infrared spectrum of the product, based on the 8.55 μ band of the contaminant (IV) (Table IV). In the two cases thus tested (runs 5 and 6, Table III), it was apparent that the extent of the contamination by ethyl hydratropate remained essentially unaltered in going from ketone III to ester V. This represents an added if indirect point in support of the accuracy of the various methods of analysis employed. The results thus realized were further confirmed by the fact that phenylmethylcarbinol, obtained by saponification of the product mixtures, had an optical purity identical, within experimental error, with that calculated for V in the mixed esters (Table III).

Taking into consideration optical purities of

(17) The contaminant evidently arises from a subsequent reaction of 3-phenyl-2-butanone and methyllithium; $cf.$, $e.g.$, C. Tegnér, $Acta$ $Chem.$ $Scand.$, **6**, 782 (1952).

TABLE IV

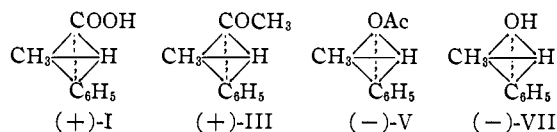| Compound	Infrared spectrum, principal bands, μ^a
3-Phenyl-2-butanone	W: 7.59, 9.65, 10.54
	M: 3.32, 6.24, 7.26, 8.35, 8.55, 9.31
	S: 5.82, 6.69, 6.88, 7.37, 14.32
Ethyl hydratropate^b	W: 6.25, 11.00, 11.58, 13.8
	M: 3.34, 6.68, 6.86, 7.25, 7.30, 7.54, 7.70, 8.05, 9.10, 9.25–9.38, 9.65
	S: 5.78, 8.30, 8.55, 14.34
Methyl hydratropate	W: 6.22, 9.66, 9.86, 10.30, 11.64
	M: 3.30, 3.35, 6.67, 7.25, 7.50, 9.06, 9.15, 13.65–13.8
	S: 5.75, 6.85, 6.96, 8.00, 8.25, 8.55, 14.32
Phenylmethylcarbinyl acetate	W: 3.28, 3.32, 7.0, 7.52, 7.66, 8.46, 11.0, 11.64–11.72
	M: 6.69, 6.88, 7.79, 10.02, 10.60
	S: 5.7–5.8, 7.30, 8.0–8.12, 8.24, 9.35, 9.69, 9.78, 14.33

^{a} Samples made up to 5 wt. % solutions in carbon tetrachloride. W(weak), M(medium), S(strong) refer to bands having 60–100%, 30–60% and 0–30% transmittance, respectively. ^{b} The material had b.p. 67° (1 mm.), $n^{25}{}_D$ 1.4946, $d^{25}{}_4$ 1.005; M_D calcd. 51.05, M_D found 51.39.

starting material and product, the retention of asymmetry in the rearrangement is complete, within experimental error (Table III). The result furnishes added justification to our earlier working hypothesis regarding the maximum rotation of 3-phenyl-2-butanone ($vide$ $supra$).

Retention of Configuration in the Rearrangement. —In the choice of 3-phenyl-2-butanone as the starting material for the oxidation, account was taken of the important fact that the compounds involved in the reaction sequence belonged to one of the most widely investigated and most thoroughly documented stereochemical families, the α-phenethyl group. Little if any doubt can attach to the configuration of (+)-I[11] and hence that of (+)-III, which was prepared from (+)-I by reactions not

affecting bonds linked to the asymmetric center. The configuration of (−)-phenylmethylcarbinol (VII) is firmly established,[18] and hence that of the derived acetate, (−)-V, is known. The assignment of these configurations is consistent with the results of recent studies, in which (+)-I and (−)-VII were both related to mandelic acid, and hence to each other.[19] It may therefore be con-

$$
\begin{array}{cccc}
\text{COOH} & \text{COCH}_3 & \text{OAc} & \text{OH} \\
\mathrm{CH_3{-}\!\!\!\diamond\!\!\!-H} & \mathrm{CH_3{-}\!\!\!\diamond\!\!\!-H} & \mathrm{CH_3{-}\!\!\!\diamond\!\!\!-H} & \mathrm{CH_3{-}\!\!\!\diamond\!\!\!-H} \\
\mathrm{C_6H_5} & \mathrm{C_6H_5} & \mathrm{C_6H_5} & \mathrm{C_6H_5} \\
(+)\text{-I} & (+)\text{-III} & (-)\text{-V} & (-)\text{-VII}
\end{array}
$$

cluded that (+)-III and (−)-V are configurationally related, and it follows that the conversion of the former into the latter proceeds with retention of configuration.

Our results, besides offering conclusive evidence for the intramolecularity of the Baeyer–Villiger rearrangement, serve to point toward this oxidative cleavage as a fairly general and elegant means for relating the configurations of acids (RCOOH) and alcohols (ROH).

Experimental[20]

Preparation and Oxidation of *dl*-3-Phenyl-2-butanone.— Hydratropoyl chloride, prepared in 95% yield from hydratropic acid by reaction with phosphorus trichloride,[21] was distilled at 75° (2 mm.) and treated with cadmium dimethyl according to the directions of Campbell and Kenyon.[12] The reaction mixture was allowed to sit overnight and subsequently neutralized by the cautious addition of ice-cold dilute sulfuric acid. The ether layer, after washing with sodium carbonate and water, was dried and distilled. The product was treated with Girard reagent-T in the usual manner, and the resulting aqueous solution extracted with ether three times in order to remove any non-ketonic fraction. After acidification, the liberated oil was dried and distilled. The ketone (50–70% yield based on starting acid) had b.p. 107–108° (22 mm.), 65° (2.3 mm.) (repd.[22,23] 106–108° (22 mm.)), n^{25}D 1.5074 (repd. n^{25}D 1.5085[22] and n^{20}D 1.5092[23]), d^{25}_4 0.975 (repd. d^{20}_4 0.9816[23]); MD calcd. 44.79, MD found 45.27 (repd. 45.03[23]). The bands of the infrared spectrum are presented in Table IV.

The semicarbazone melted at 173° (repd. m.p. 172–173°[24]).

A solution of perbenzoic acid (PBA) in chloroform was prepared as described by G. Braun.[25] A dry solution of PBA (1.30 equiv.) in chloroform (147 ml.) was added slowly to 8.01 g. (0.0541 mole) of ketone, constant agitation being maintained throughout the addition. After standing in the dark at room temperature for 65 hours, the mixture was extracted five times with cold 10% sodium hydroxide, washed with water till the washings were neutral, dried with sodium sulfate, stripped of chloroform under reduced pressure, and distilled to furnish 7.75 g. (87%) of a sweet-smelling liquid, b.p. 98–101° (13 mm.), n^{25}D 1.4953. Treatment with Girard reagent-T to remove unreacted ketone afforded, after redistillation, 6.1 g. of a liquid whose infrared spec-

trum was identical in every respect with that of an authentic sample of phenylmethylcarbinyl acetate (b.p. 73° (2.5 mm.), n^{25}D 1.4929, d^{25}_4 1.015; MD calcd. 46.43, MD found 47.00) and distinctly different from that of an authentic sample of methyl hydratropate (b.p. 79° (3.3 mm.), n^{25}D 1.5005 (repd. n^{25}D 1.5027[26]), d^{25}_4 1.039; MD calcd. 46.43, MD found 46.53); cf. Table IV.

Preparation and Saponification of (+)-Phenylmethylcarbinyl Acetate.— A sample of this acetate, α^{26}D +35.82° (l 1, homogeneous), n^{25}D 1.4942, was obtained in 88% yield from the reaction of C.P. acetic anhydride and phenylmethylcarbinol, $[\alpha]^{27}$D +12.60° (homogeneous), 29.0% optically pure,[27] n^{25}D 1.5260. Subsequent treatment with Girard reagent-T gave acetate, α^{26}D +36.98° (l 1, homogeneous), n^{25}D 1.4930. The change in properties after this treatment is indicative of the presence of about 3% of acetophenone in the original carbinol.[28] A sample of this acetate (3.7 g.) was saponified by refluxing for 35 minutes with 20 ml. of 50% ethanol–water containing 3.0 g. of potassium hydroxide. The hydrolysis mixture was worked up to yield 2.2 g. (80%) of phenylmethylcarbinol, n^{25}D 1.5257, $[\alpha]^{25}$D +12.55° (homogeneous). It is concluded that no racemization occurs under the conditions of the saponification.

The maximum rotation of the acetate, by extrapolation to 100% optical purity, is $[\alpha]$D 126.1° (homogeneous) (repd. $[\alpha]$D 121.3° (homogeneous[29])).

Optically Active 3-Phenyl-2-butanone.— Hydratropic acid was resolved by crystallization of its strychnine salt,[10] and its optical purity for each run determined by comparison of its rotation with the maximum reported rotation, neat or in solution.[10,30] The ketones were prepared either (A) by reaction of hydratropoyl chloride and cadmium dimethyl, or (B) by reaction of the acid and methyllithium.

(A).— The preparation was the same as that for the *dl*-compound (*vide supra*), with the important exception that the ketone was not purified via its Girard reagent-T derivative. It is known that this method leads to appreciable racemization[8] and it would seem to be particularly unsuitable to the easily racemized ketone studied in this work. The results of eleven runs are summarized in Table I. The two products codistilled over very short ranges, near 110° (20 mm.), regardless of their respective quantities. A typical calculation, of the type found in Table I, is given for run no. 1. The product had n^{25}D 1.5031, or 0.0043 less than that of 3-phenyl-2-butanone (III). The fraction of ethyl hydratropate (IV) in the mixture was therefore 0.0043/0.0158, or 27.2%. Assuming that the maximum rotation of IV is αD 36.5° (l 0.5, homogeneous)[31] and granting that the optical purity of the starting hydratropic acid is 87.1%, the maximum contributing rotation of IV is 36.5 (0.871) (0.272) or 8.65°, leaving, by difference, +51.7° as attributable to III, the rotation of the mixture being +60.4°. Correcting to l = 0.5, this rotation becomes 51.7 (100/72.8) or +71.0⁵ (l 0.5, homogeneous). Comparison of this with the maximum rotation of the ketone, αD 164.5° (l 0.5, homogeneous), gives 43.2% as the optical purity of the ketone. Since the starting material was 87.1% active, the extent of racemization is (87.1 − 43.2)/87.1 or 50.4%.

The greatest racemization occurred in the (−)-fractions which concentrated contaminant α-phenylisobutyric acid. In several cases it was necessary to treat the product with ammonia immediately after isolation in order to freeze the steady racemization which was induced by a strongly acidic by-product, possibly hydrogen chloride, present in the distillate. In one instance the optically active product had a

(18) P. A. Levene and S. A. Harris, *J. Biol. Chem.*, **113**, 55 (1936); P. A. Levene and P. G. Stevens, *ibid.*, **89**, 471 (1930).

(19) K. Mislow, THIS JOURNAL, **73**, 3954 (1951); K. Mislow and M. Heffler, *ibid.*, **74**, 3668 (1952).

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(30) For temperatures other than 16°, estimates were made by inter- or extrapolation on the basis of the observation that for a sample with α^{16}D +181.43° (l, 2, homogeneous), α^{25}D was +172.00° (l, 2, homogeneous).

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half-life of only 45 minutes, its rotation decreasing from αD −43° (l 0.5, homogeneous) to −3° after three hours. In run no. 7 from 20 g. of hydratropic acid as the starting quantity, there was obtained 1.06 g. of a white solid when the ether layer was washed with ammonia. Recrystallized from ethanol–water, the solid had m.p. 160–160.5° (repd. for α-phenylisobutyramide 160–161°).[32]

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.62; H, 8.03; N, 8.58. Found: C, 73.64; H, 7.82; N, 8.30.

In run no. 11, a high-boiling product (1.5 g. from 10 g. of hydratropic acid as the starting quantity), b.p. 135–200° (10 mm.), on standing turned purple and partially solidified. Recrystallized from petroleum ether, the solid, which was soluble in sodium carbonate, had m.p. 78.5–79.0° (repd.[32,16a] for α-phenylisobutyric acid 77–78° and 80–81°[33]).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.26; H, 7.12.

(B).—From preliminary runs it appeared that the addition of hydratropic acid to the theoretical quantity (two moles) of methyllithium gave yields of ketone varying from 10 to 55%. The product was usually contaminated, to judge by the high refractive index, and always racemized to a variable (30–70%) extent. Increased (up to four) mole ratios of methyllithium gave improved results.

To 0.20 mole of methyllithium in 225 ml. of ether was added 7.5 g. (0.050 mole) of 89.8% optically pure hydratropic acid (α^{28}D +43.50° (l 0.5, homogeneous) and [α]^{27}D +82.5° (c 2.23, benzene)) over a period of 20 minutes at room temperature (run no. 12, Table II). Stirring was continued for 20 more minutes, and the solution was then poured into ice-water. The ether layer was washed four times with water (until washings were neutral), dried over sodium sulfate, and distilled, to give 6.8 g. of a liquid, b.p. 77° (1 mm.), n^{25}D 1.5087, α^{27}D +102.7° (l 0.5, homogeneous). Slow fractionation gave fraction I, b.p. 79–80° (5 mm.), 1.49 g., n^{25}D 1.5072, αD +133.16° (l 0.5, homogeneous); fraction II, b.p. 80–81° (5 mm.), 1.96 g., n^{25}D 1.5077, αD +124.4° (l 0.5, homogeneous); fraction III, b.p. 81–84° (5 mm.), 1.87 g., n^{25}D 1.5087, αD +107.4° (l 0.5, homogeneous); and a residue, 1.20 g., n^{25}D 1.5128. The contaminant was assumed to be 2-methyl-3-phenyl-2-butanol because the original liquid gave a Lucas test for a tertiary carbinol yet did not form a phthalate derivative under ordinary conditions.[34] The reported rotation of the carbinol

is very low.[35] Fraction I had an infrared spectrum identical with that of *dl*-3-phenyl-2-butanone; it was about 10% racemized.

Other significant preparations are listed in Table II. In runs no. 13, 15 and 16, the product was treated with semicarbazide acetate and the precipitated semicarbazone subjected to steam distillation in the presence of phthalic anhydride[8] in order to recover chemically pure 3-phenyl-2-butanone.

(+)-3-Phenyl-2-butanone Semicarbazone.—A solution of 376 mg. of semicarbazide hydrochloride and 500 mg. of sodium acetate in 3.5 ml. of water was added to 485 mg. of 87.1% active (+)-3-phenyl-2-butanone (run no. 2, Table I) dissolved in 3.0 ml. of 95% ethanol. Slow crystallization gave 560 mg. (84%) of solid. Four crystallizations from 95% ethanol gave 140 mg. of white prisms, m.p. 180–181°, [α]^{24}D +117.8° (c 1.67, chloroform).

Oxidation of Optically Active 3-Phenyl-2-butanone.—The procedure followed was that described for the inactive ketone, with the exception that the period of reagent contact was shortened to 43 hours; the results are summarized in Table III. In run no. 10, 4.41 g. of ketone (optical purity 32.3%), a sample of which gave a semicarbazone, m.p. 163–167°, [α]^{25}D +39.0° (c 1.73, chloroform), upon oxidation yielded a product, 4.42 g., b.p. 52–68° (0.3 mm.), n^{25}D 1.4956, α^{25}D −14.24° (l 0.5, homogeneous). The latter was dissolved in a small volume of ethanol, treated with a solution of 1 g. of semicarbazide hydrochloride and 2 g. of sodium acetate in 20 ml. of water, and the mixture was concentrated and distilled. The product, 3.03 g. of liquid, had b.p. 101° (16 mm.), n^{25}D 1.4934, α^{25}D −19.00° (l, 0.5, homogeneous), which changed to α^{25}D −19.75° subsequent to treatment with Girard reagent-T. The residue from the distillation consisted of a white solid, which upon recrystallization from ethanol yielded 200 mg. of semicarbazone, m.p. 161–165°, [α]^{27}D +40.2° (c 1.95, chloroform). This experiment is indicative of the substantial absence of racemization of the ketone during the oxidation.

In two instances (runs 5 and 10) the acetate ester was hydrolyzed to phenylmethylcarbinol; the procedure was that described for the inactive acetate.

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Migration Aptitudes in the Stieglitz Rearrangement[1]

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Approximate migration aptitudes for the *p*-methoxyphenyl (9.1), *p*-chlorophenyl (0.55) and *p*-nitrophenyl (0.38 to 0.18) groups have been determined by a study of the Stieglitz rearrangements of appropriately substituted triarylmethylhydroxylamines.

Previous quantitative studies of migration aptitudes of aryl groups have been confined mainly to reactions in which the group migrates from one carbon to an adjacent carbon.[2] We thought it of interest to study migration aptitudes in which the migration proceeds from carbon to nitrogen.

Preliminary experiments were directed toward a reaction of triarylcarbonium ions in sulfuric acid with sodium azide. However, when it was found that only triphenylmethyl azide resulted

from the reaction of triphenylcarbinol with sodium azide and sulfuric acid,[3] this approach was abandoned. Attention was next directed toward the rearrangement of triarylmethylhydroxylamines, the Stieglitz rearrangement.[4] A study of previous work revealed that the substitution of a chlorine or bromine atom in the para position had little effect on the migration aptitude of a phenyl group.

(1) Taken from the Ph.D. thesis of P. M. Hay, Ohio State University, 1952.

(2) H. Adkins in H. Gilman's "Organic Chemistry," Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1937, p. 1068.

(3) C. L. Arcus and R. J. Mosley, *Chemistry and Industry*, 701 (1951), reported the same result.

(4) C. W. Porter, "Molecular Rearrangements," Chemical Catalog Co. (Reinhold Publ. Corp.), New York, 1928, pp. 30–34, and references therein.