46. *Retention of Asymmetry during the Curtius and the Beckmann Change.*

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(+)Hydratropic azide is converted by the Curtius rearrangement into (−)α-phenylethylamine with 99·3% retention of optical purity. The previously observed loss of 4·2% in optical purity during the analogous Hofmann rearrangement may be connected with the known racemisation of *iso*cyanates by alkalis. The oxime of (−)*methyl γ-heptyl ketone* undergoes the Beckmann transformation into (+)*aceto-γ-heptylamide*, apparently in an optically pure condition. Evidence is therefore presented that the Curtius and the Beckmann reaction also are true intramolecular rearrangements.

It is now possible to show that in the Hofmann, Curtius, Lossen, Beckmann, sulphinate, and (probably) alkylphenol rearrangements, the migrating group ·Cabc retains its relative configuration during transfer.

(I) A RECENT investigation (Arcus and Kenyon, J., 1939, 916) has shown that optically active hydratropamide, $CHMePh{\cdot}CO{\cdot}NH_2$, is converted by the Hofmann rearrangement into α-phenylethylamine with an average retention of 95·8% of optical activity. We now find that from the analogous Curtius rearrangement of the azide of (+)hydratropic acid is obtained (−)α-phenylethylamine of no less than 99·3% optical purity. In both these reactions the sign of rotation of the amine is the opposite of that of the original hydratropic acid.

The present result renders it probable that in the Curtius reaction no racemisation at all takes place during the migration of the optically active –CHMePh group, the observed loss of 0·7% probably being covered by experimental errors occasioned by the high temperature coefficients of the rotatory powers of the compounds concerned. A difference is therefore to be noted between the two rearrangements, as the 4·2% loss in optical purity observed by Arcus and Kenyon is real and outside the experimental error. In view of the close similarity between the Hofmann and the Curtius reaction, it seems unlikely that, in the former, migration is accompanied by the dissociation of a proportion of free –CHMePh radicals to bring about the observed racemisation. Some light is, however, cast on this phenomenon by Wallis and Dripps' observation (*J. Amer. Chem. Soc.*, 1933, **55**, 1701) that (+)α-benzylethyl *iso*cyanate was hydrolysed in acid solution to (+)α-benzylethylamine hydrochloride with no apparent racemisation, but that on alkaline hydrolysis it gave *dl-NN'*-bis-α-benzylethylurea. This suggests that, like optically active disubstituted acetic esters, *iso*cyanates of the type $CHRR'{\cdot}N{:}C{:}O$, which are intermediates in both the reactions under discussion, suffer racemisation in presence of an alkaline reagent such as is used to bring about the Hofmann reaction. In the Curtius reaction, on the other hand, the free *iso*cyanate is obtained directly without the action of a reagent and in the present instance was hydrolysed to the amine by means of hydrochloric acid.

The observed racemisation of *iso*cyanates by alkalis further strongly suggests that, as in the case of carboxylic esters (cf. Kenyon and Young, J., 1939, 216), these compounds under the influence of bases lose a proton from the α-carbon atom.

From these considerations it appears that during both the Hofmann and the Curtius

rearrangement, asymmetry of the migrating group –CHMePh is maintained quantitatively, thereby providing strong evidence that these reactions are truly intramolecular, and, in fact, that electron-sharing between the migrating group and the rest of the molecule is continuous throughout.

(II) We have also examined the stereochemical course of the Beckmann transformation of an optically active ketoxime CHRR'·CMe:NOH into the substituted acetamide CHRR'·NH·COMe.

The Beckmann change is a spontaneous rearrangement of oxime esters (of strong acids) or salts of oximes or their esters; the rearrangement of the oximes themselves by means of various reagents probably takes place through the medium of one of these compounds (Blatt, *Chem. Rev.*, 1933, **12**, 215; Watson, "Modern Theories of Organic Chemistry," 1937, p. 139):

$$\mathrm{R{\cdot}\underset{\underset{\mathrm{NOH}}{\|}}{C}{\cdot}R'} \longrightarrow \mathrm{R{\cdot}\underset{\underset{\mathrm{NOX}}{\|}}{C}{\cdot}R'} \xrightarrow{\text{direct}} \mathrm{XO{\cdot}\underset{\underset{\mathrm{NR}}{\|}}{C}{\cdot}R'} \xrightarrow{H_2O} \mathrm{O{=}\underset{\underset{\mathrm{NHR}}{|}}{C}{\cdot}R'}$$

Entry of the migrating group into a foreign molecule has never been observed, but at present the only direct piece of evidence that the migrating group is never kinetically free is provided by an interesting ring enlargement carried out by Ruzicka and his co-workers (*Helv. Chim. Acta*, 1933, **16**, 1323):

$$\mathrm{[CH_2]_{13}}\begin{cases}\mathrm{C{=}NOH}\\ \mathrm{CH_2}\end{cases} \longrightarrow \mathrm{[CH_2]_{13}}\begin{cases}\mathrm{CO{-}NH}\\ \mathrm{CH_2}\end{cases}$$

If the ring were opened during the transformation, it would only close again to an extremely limited extent.

For the purpose of this investigation an optically active ketone of the type CHRR'·COMe was required. An attempt to resolve methyl β-butyl ketone directly by means of an alkaloidal salt of its o-*carboxyphenylhydrazone* was unsuccessful, and recourse was made to synthesis from the corresponding optically active acid CHRR'·CO_2H. Accordingly, the bromide of (—)ethyl-*n*-butylacetic acid was treated with dimethylcadmium in ethereal solution (Gilman and Nelson, *Rec. Trav. chim.*, 1936, **55**, 518), affording (—)*methyl γ-heptyl ketone*, which was converted into its dextrorotatory oxime. On treatment with phosphorus pentachloride the oxime underwent rearrangement to dextrorotatory *aceto-γ-heptylamide*, $[\alpha]^{21°}_{5461}$ + 1·4°, $[\alpha]^{21°}_{4358}$ + 5·3° (in alcohol). The constitution of the last compound was confirmed by synthesis of the corresponding dl-*amide*, by acetylating dl-*γ-heptylamine* obtained from *dl*-ethyl-*n*-butylacetamide by the Hofmann reaction; the product was identical with that from the dl-*oxime*, which therefore has the *anti*-heptyl structure. This observation is in harmony with the results of Bachmann and Barton (*J. Org. Chem.*, 1938, **3**, 300), who found that stable ketoximes were generally *anti*- with respect to the heavier group.

By using a partly resolved (+)ethylbutylacetic acid, a (—)aceto-γ-heptylamide was obtained similarly, having $[\alpha]^{21°}_{5461}$ — 0·7°, $[\alpha]^{21°}_{4358}$ — 1·2°. Starting from the same acid, the last compound was also obtained *via* γ-heptylamine as above, and this had $[\alpha]^{21°}_{5461}$ — 0·6°, $[\alpha]^{21°}_{4358}$ — 2·0°. Too much quantitative significance should not be given to these low rotations, but they are sufficient to determine the configurational relationships involved. Some evidence was obtained, however, that the *l*(+)aceto-γ-heptylamide must have been nearly optically pure, as it melted fairly sharply at 43—44·5°, whereas the partly active (—)amide melted lower and more indefinitely at 30—40°. (The *dl*-amide had m. p. 52—53°.)

The Beckmann transformation therefore falls into line with the rearrangements considered in the first part of this paper, in that asymmetry of the migrating group –CHRR' is substantially preserved, thus providing further proof that the reaction is intramolecular.

Retention of Configuration during Intramolecular Changes.—The Hofmann and the Curtius reaction have for some time been regarded as proceeding with retention of configuration on the part of the migrating radical ·Cabc (Wallis and Nagel, *J. Amer. Chem. Soc.*, 1931, **53**, 2787; Braun and Friehmelt, *Ber.*, 1933, **66**, 684), and very recently Archer (*J. Amer.*

Chem. Soc., 1940, **62**, 1872) has pointed out an experimental proof that this is actually true. Scrutiny of the literature provides another proof. Wallis and Nagel (*loc. cit.*) converted (+)benzylmethylacetic acid into the (+)amide and thence into (+)α-benzylethylamine hydrochloride; the same result had been obtained *via* the (+)azide (Jones and Wallis, *ibid.*, 1926, **48**, 169). Now, it has also been established (Kenyon, Phillips, and Pittman, J., 1935, 1072) that (−)benzylmethylacetic acid has the same configuration as (−)α-benzylethylamine hydrochloride [from the (+)amine], each being produced from (+)α-benzylethyl *p*-toluenesulphonate by a series of reactions involving one Walden inversion. Therefore, the (+)α-benzylethylamine obtained from the Hofmann and the Curtius reaction had the same configuration as the original (+)benzylmethylacetamide or azide respectively. It will further be seen from the present work that α-phenylethylamine has the same configuration whether it is obtained through the Hofmann or the Curtius rearrangement.

It may also be noted that Wallis and his co-workers (Wallis and Dripps; Jones and Wallis; *locc. cit.*) obtained *N*-α-benzylethylurea of the same rotatory power and sign of rotation, either by the Curtius rearrangement or by the Lossen rearrangement of the corresponding hydroximic benzoate, starting in each case from the same (+)benzylmethylacetic acid.

Since it may now be presumed that (+)γ-heptylamine and its (−)acetyl derivative have the same configuration as (+)ethylbutylacetic acid and (−)methyl γ-heptyl ketoxime, it follows that the Beckmann rearrangement also does not involve a Walden inversion. Arcus, Balfe, and Kenyon (J., 1938, 485) have previously observed that relative configuration was retained during the intramolecular conversion of (−)phenylmethylcarbinyl *p*-toluenesulphinate into the corresponding sulphone.

Sprung and Wallis (*J. Amer. Chem. Soc.*, 1934, **56**, 1715) have described the rearrangement of (+)phenyl β-butyl ether into (+)*o*-β-butylphenol. This ether has been configurationally related to (+)β-butylbenzene (Kenyon, Phillips, and Pittman, *loc. cit.*), and it is reasonable to assume that (+)*o*-β-butylphenol has the same configuration as (+)β-butylbenzene, leading to the conclusion that in this reaction, too, the migrating radical is transferred without inversion.

The general conclusion is therefore reached that where an optically active radical Cabc undergoes transference in an intramolecular change, it retains its configuration as well as its asymmetry.

In the last two rearrangements mentioned, at any rate, the asymmetric carbon atom almost certainly undergoes a replacement of one of its electron pairs during its transfer, so that if the reaction were entirely parallel to the corresponding nucleophilic substitution, an inversion would be expected. Ingold and his collaborators (J., 1937, 1259) have discussed the question briefly without reference to experimental evidence, and concluded that in intramolecular processes of this nature an inversion does not take place where it is rendered difficult or impossible for steric reasons. The observed retention of configuration is therefore an excellent proof that these reactions are truly intramolecular (Hammett, " Physical Organic Chemistry," New York, 1940, p. 327; cf. also Gilbert and Wallis, *J. Org. Chem.*, 1940, **5**, 184).

In rearrangements of the Hofmann and the Beckmann type, the migrating carbon atom can be formulated as carrying its full octet throughout its transference, so that on the analogy of an electrophilic substitution an inversion is not to be expected (cf. Nevell, de Salas, and Wilson, J., 1939, 1188); this view is in harmony with the ease with which these reactions take place, in contrast to the sulphinate and phenyl ether rearrangements which show a strong tendency to proceed by *inter*molecular paths and to lead to by-products.

Experimental.

Conversion of the Azide of (+)Hydratropic Acid into (−)α-Phenylethylamine.—(i) A mixture of (+)hydratropic acid (5·5 g.) and phosphorus trichloride (2·0 g.) was kept at 60—65° for an hour and then cooled; the upper layer of hydratropoyl chloride was poured into a suspension of sodium azide (10 g., freshly precipitated from its aqueous solution by acetone) in dry ether, and the mixture stirred for 24 hours. The filtered solution had a pronounced odour of *iso*-

cyanate and on gentle warming evolved a steady stream of gas; when the reaction had become slow the ether was removed, and concentrated hydrochloric acid added to the oily residue, whereupon there was a renewed evolution of gas. The mixture was heated at about 50° until the reaction had ceased, diluted with water, and extracted with ether. The amount of recovered hydratropic acid was too small to distil. The hydrochloric acid solution was rendered alkaline and extracted with ether; the dried (sodium hydroxide) and evaporated solution yielded (−)α-phenylethylamine (3 c.c.), b. p. 70°/12 mm., $\alpha_{5461}^{16°}$ − 22·76° (*l*, 0·5), which value is 99·3% of that for the optically pure (−)amine ($\alpha_{5461}^{16·5°}$ − 22·92°; Ingold and Wilson, J., 1933, 1503); acetyl derivative, m. p. 103—104°.

(ii) In a preliminary experiment using (−)hydratropic acid (7·5 g., of $\alpha_{5893}^{15°}$ − 14·96°; *l*, 0·5), where the stirring with sodium azide was not so efficient, there were obtained (+)α-phenylethylamine (3 g.), b. p. 69·5°/12 mm., $\alpha_{5461}^{17°}$ + 6·92° (*l*, 0·5), and unreacted (−)hydratropic acid (3·0 g.).

l(−)*Methyl γ-Heptyl Ketone*. [The *l*-configuration is arbitrarily assigned to (−)ethyl-*n*-butylacetic acid.]—*l*(−)Ethyl-*n*-butylacetic acid of $\alpha_{5461}^{21°}$ − 4·38°· (Kenyon and Platt, J., 1939, 633) was converted into its (−)bromide, b. p. 97—98°/15 mm., $n_D^{19°}$ 1·4617, $d_{4°}^{20°}$ 1·1927, by warming with phosphorus tribromide and redistilling the top layer. A small portion of this on treatment with concentrated aqueous ammonia yielded *l*(−)ethyl-*n*-butylacetamide, crystallising from water in fine needles, m. p. 98° (rotatory powers in the table). The dl-*bromide*, prepared similarly, had b. p. 97°/19 mm., $n_D^{18°}$ 1·4612, $d_{4°}^{20°}$ 1·1904 (Found, by hydrolysis: *M*, 210; Br, 38·3. $C_8H_{15}OBr$ requires *M*, 207; Br, 38·6%).

To an ethereal solution of dimethylcadmium (Gilman and Nelson, *loc. cit.*), obtained by treating methylmagnesium bromide (from 1·6 g. of metal) with anhydrous cadmium dibromide (9 g.), was added the (−)ethylbutylacetyl bromide (9 g.). After 2 hours' refluxing and standing overnight, water and a little dilute acid were added, and the product steam-distilled. By extraction of the distillate l(−)*methyl γ-heptyl ketone* was obtained as a colourless mobile liquid with a peculiar sickly smell, b. p. 63—64°/9 mm., $n_D^{15°}$ 1·4228, $d_{4°}^{20°}$ 0·8318, $\alpha_{5461}^{18°}$ − 0·26° (*l*, 0·5) (other rotatory powers in the table). Yield 65%. It did not give good analytical figures (Found: C, 74·4; H, 12·5. $C_9H_{18}O$ requires C, 76·0; H, 12·75%), but this was traced to the formation of a high-boiling product, b. p. 101—104°/5 mm., during distillation. The *dl*-ketone had b. p. 73°/15 mm., 176—179°/760 mm.; $n_D^{15°}$ 1·4223; $d_{4°}^{20°}$ 0·8246.

The corresponding acid chloride was found to react incompletely with dimethylcadmium under the above conditions.

Beckmann Transformation of l(+)*Methyl γ-Heptyl Ketoxime*.—The *l*-ketone (3·3 g.) was boiled under reflux in aqueous-alcoholic solution with hydroxylamine hydrochloride (1·7 g.), sodium acetate (4·3 g.) being added in portions during about ½ hour. On dilution and extraction with ether, the oily l(+)methyl *anti*-γ-heptyl ketoxime was obtained, b. p. 111—113°/12 mm., $n_D^{16°}$ 1·4502, $d_{4°}^{20°}$ 0·8840, $\alpha_{5461}^{21°}$ + 0·39° (*l*, 0·5). It was treated with phosphorus pentachloride (5 g.) in dry ether, and after gentle warming to dissolve all the reagent, the solvent was distilled off. The liquid residue was decomposed by addition of ice, and the washed and dried (sodium sulphate) ethereal extract yielded l(+)*aceto-γ-heptylamide*, which was purified by distillation; it had b. p. 143—145°/15 mm., and solidified to a mass of needles, m. p. 43—44·5°. In alcoholic solution this had the rotations given in the table below (Found: N, 9·0. $C_9H_{19}ON$ requires N, 8·9%).

Table of Specific Rotatory Powers.

Compound.	State.	*t*.	$[\alpha]_\lambda$. λ=6438.	5893.	5780.	5461.	4358.
l-Ethyl-*n*-butylacetyl bromide	Homog.	20°	−0·30°	−0·36°	−0·39°	−0·44°	−0·97°*
	In Et_2O; *c*, 7·069	20	−0·4	−0·7	−1·1	−1·2	−6·0*
l-Methyl γ-heptyl ketone	Homog. ($d_{4°}^{18°}$ = 0·8399)	18	−0·42	−0·56	−0·57	−0·61	−1·42
	In EtOH; *c*, 5·313	21	−0·5	−0·7	−0·8	−0·9	−1·5
l-Methyl γ-heptyl ketoxime	Homog.*	21	+0·33	+0·38	+0·66	+0·87	+3·41
	In Et_2O; *c*, 5·000	20	+0·1	+0·1	+0·3	+0·3	+1·3
l-Aceto-γ-heptylamide	In EtOH; *c*, 4·001 †	21	+0·9	+1·0	+1·2	+1·4	+5·3
l-Ethyl-*n*-butylacetamide	In EtOH; *c*, 2·340 †	20	−1·3	−2·9	−3·1	−3·9	−6·8

* *l*, 0·5. † *l*, 1·0. All others are *l*, 2.

Synthesis of dl- *and* (−)*Aceto-γ-heptylamide*.—(a) Via *γ-heptylamine*. *dl*-Ethyl-*n*-butylacetic acid was converted by phosphorus trichloride into its chloride, b. p. 68°/13 mm. (Tiffeneau,

Bull. Soc. chim., 1923, **33**, 185, gives b. p. 85—90°/20 mm.), which on treatment with aqueous ammonia (*d* 0·880) gave the *dl*-amide, short needles (from hot water), m. p. 102° (Raper, J., 1907, **91**, 1837, gives 101—102°). 21 G. of this amide were added to a solution of bromine (8 c.c.) in sodium hydroxide (25 g. in 150 c.c. of water). After ½ hour's warming, dl-*γ-heptylamine* had separated, which after extraction with ether and drying over potassium hydroxide had b. p. 140—142°, $n_D^{19°}$ 1·4224, $d_4^{20°}$ 0·7781 (Found: N, 12·1. $C_7H_{17}N$ requires N, 12·2%); its *hydrochloride* crystallised from ethyl acetate in small needles, m. p. 169—170° (Found: Cl, 23·1. $C_7H_{17}N,HCl$ requires Cl, 23·5%). Warming the amine with acetyl chloride and addition of water afforded dl-*aceto-γ-heptylamide*, which was recrystallised, with some difficulty, by dissolving it in a little acetic acid and adding water; it formed needles, m. p. 52—53° (Found: N, 8·2. $C_9H_{19}ON$ requires N, 8·9%).

A partly active (+)ethyl-*n*-butylacetic acid, α_{5893} + 0·53° (*l*, 0·25), was converted by similar methods successively into the (+)chloride, b. p. 86—89°/21 mm., $n_D^{19°}$ 1·4339, $d_4^{21°}$ 0·9468, $\alpha_{5461}^{20°}$ + 0·94° (*l*, 2) (Found: Cl, 21·5; *M*, 165. Calc. for $C_8H_{15}OCl$: Cl, 21·8%; *M*, 163); (+)amide, m. p. 100—101°, $[\alpha]_{4561}^{20°}$ + 0·7° (in alcohol) (not recrystallised); (+)*γ*-heptylamine, b. p. 140—142°, $n_D^{19°}$ 1·4188, $\alpha_{5461}^{21°}$ + 0·15° (*l*, 0·25); and *d* + *dl*(−)aceto-*γ*-heptylamide, b. p. 140—145°/15 mm., m. p. 35—45°, $[\alpha]_{5893}^{21°}$ − 0·8, $[\alpha]_{5461}^{21°}$ − 0·6°, $[\alpha]_{4358}^{21°}$ − 2·0° (*c*, 1·969; *l*, 1) in ethyl alcohol.

(b) Via *the Beckmann rearrangement*. The *dl*-ketone yielded an *oxime*, b. p. 113—114°/13 mm., $n_D^{14°}$ 1·4525, $d_4^{25°}$ 0·8822 (Found: N, 8·5. $C_9H_{19}ON$ requires N, 8·9%). Treatment of the oxime (4 g.) in ether with 6 g. of phosphorus pentachloride gave crude *dl*-aceto-*γ*-heptylamide, m. p. 42—46°, which after three recrystallisations was raised to 50—52° alone or mixed with the product from (a).

The same (+)ethylbutylacetic acid was also converted through its (+)bromide [b. p. 112—113°/24 mm., $n_D^{19°}$ 1·4599, $\alpha_{5461}^{20°}$ + 0·15° (*l*, 2)] into a (+)methyl heptyl ketone, b. p. 71°/13 mm., $n_D^{15°}$ 1·4228, $\alpha_{5461}^{18°}$ + 0·12° (*l*, 2), the *d* + *dl*-oxime [b. p. 116—117°/15 mm., $n_D^{19°}$ 1·4522, $\alpha_{5461}^{20°}$ − 0·05° (*l*, 0·25)] of which was subjected as before to the Beckmann reaction, giving *d* + *dl*(−)aceto-*γ*-heptylamide, b. p. 148—150°/17 mm., m. p. 30—40°. This had $[\alpha]_{5893}^{21°}$ − 0·7°, $[\alpha]_{5780}^{21°}$ − 0·7°, $[\alpha]_{5461}^{21°}$ − 0·7°, $[\alpha]_{4358}^{21°}$ − 1·2° in alcohol (*c*, 5·046; *l*, 2), and its rotation was also observed in the molten (supercooled) condition: it had $\alpha_{5893}^{20°}$ − 0·48°; $\alpha_{5780}^{20°}$ − 0·53°; $\alpha_{5461}^{20°}$ − 0·62°; $\alpha_{4358}^{20°}$ − 1·00° (*l*, 0·5).

Attempted Resolution of Methyl β-Butyl Ketone.—*o*-Carboxyphenylhydrazine hydrochloride (Heller and Jacobsohn, *Ber.*, 1921, **54**, 1115) was best converted into the base by dissolution in concentrated alkali and acidification with acetic acid at 0°. Warming of equivalent quantities of the base and *dl*-methyl β-butyl ketone in 75% alcohol gave the *hydrazone*, dull yellowish-white, narrow plates from light petroleum (Found: N, 11·8. $C_{13}H_{18}O_2N_2$ requires N, 12·0%). In methyl-alcoholic solution this readily afforded a strychnine salt, m. p. 172—173°, and fractional crystallisation of the latter gave, after decomposition, dextro- and lævo-rotatory hydrazones, having $[\alpha]_{5461}^{15°}$ + 3·3° and − 4·7° respectively. However, further experiments indicated that separation was irregular, apparently depending on the speed of separation of the diastereoisomerides rather than a genuine difference in solubility.

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