9. *Retention of Asymmetry During the Beckmann, Lossen, and Curtius Changes.*

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(i) The oxime of (+)-α-phenylethyl methyl ketone undergoes the Beckmann transformation into (—)acet-α-phenylethylamide with almost complete retention of asymmetry.

(ii) (+)Phenylmethylacethydroxamic acid is converted by the Lossen change into (—)-α-phenylethylamine of 99·2% optical purity.

(iii) By Schmidt's modification of the Curtius reaction (+)hydratropic acid is converted into (−)-α-phenylethylamine of 99·6% optical purity.

It is suggested that molecular configuration and asymmetry are retained during these reactions.

It was shown recently that the oxime of (−)methyl γ-heptyl ketone is converted by the Beckmann transformation into (−)acetoheptylamide in what was considered to be an almost optically pure condition (Kenyon and Young, *J.*, 1941, **263**). Unfortunately, the optical rotatory powers of these compounds are small, a fact to which attention has been directed by Bernstein and Wallis (*J. Org. Chem.*, 1942, **7**, 262), and it seemed desirable to repeat the reaction with compounds possessing higher rotatory powers.

This has been done, and the following conclusions can be drawn from the results of the work. (i) (+)-α-*Phenylethyl methyl ketoxime* having $[\alpha]_D$ +25·4° (alcohol) is converted smoothly into (−)acet-α-phenylethylamide having $[\alpha]_D$ −167·4° (alcohol); this is in close agreement with $[\alpha]_D$ −168·1°, the specific rotatory power of the optically pure compound obtained by acetylation of (−)-α-phenylethylamine prepared by direct resolution of the *dl*-base. (ii) (+)Hydratropic acid is smoothly converted successively into (+)*phenylmethylacethydroxamic acid*, (+)*benzoyl phenylmethylacethydroxamate*, and potassium benzoyl phenylmethylacethydroxamate. The last compound suspended in boiling benzene decomposes readily to give (+)-α-phenylethyl *iso*cyanate, which, on hydrolysis, yields (−)-α-phenylethylamine having an optical purity of 99·2%. (iii) The azide of (+)hydratropic acid is converted by the Curtius rearrangement into (−)-α-phenylethylamine of 99·3% optical purity (Kenyon and Young, *loc. cit.*). This reaction has been repeated by the more convenient procedure devised by Schmidt (*Ber.*, 1922, **55**, 1571), *i.e.* the addition of sodium azide to a solution of (+)hydratropic and sulphuric acids in chloroform, followed by warming. In this case the resultant (−)-α-phenylethylamine had an optical purity of 99·6%.

Since it has been shown that (+)hydratropamide is converted by the Hofmann reaction into (−)-α-phenylethylamine of 95·9% optical purity (Arcus and Kenyon, *J.*, 1939, 916) it follows that (+)hydratropic acid can be converted into (−)-α-phenylethylamine by several well-known types of molecular rearrangements with almost complete retention of asymmetry.

		Retention of optical activity.	Name of reaction.
(+)Ph·CHMe·CO$_2$H	⟶ Ph·CHMe·CO·N$_3$ ⟶ (−)-Ph·CHMe·NH$_2$	99·3%	Curtius
	⟶ Ph·CHMe·CO·N$_3$ ⟶ (−)-Ph·CHMe·NH$_2$	99·6	Schmidt
	⟶ Ph·CHMe·CO·NH$_2$ ⟶ (−)-Ph·CHMe·NH$_2$	95·8	Hofmann
	⟶ Ph·CHMe·C(:NOH)OH ⟶ (−)-Ph·CHMe·NH$_2$...	99·2	Lossen
	⟶ Ph·CHMe·C(:NOH)Me ⟶ (−)-Ph·CHMe·NHAc	99·6	Beckmann

It has been shown that the closely related (+)-benzylmethylacetic acid is converted by (*a*) the Hofmann reaction (Wallis and Nagel, *J. Amer. Chem. Soc.*, 1931, **53**, 2787) and (*b*) the Curtius reaction (Jones and Wallis, *ibid.*, 1926, **48**, 169) into (+)-α-benzylethylamine hydrochloride. It has also been shown that (−)-benzylmethylacetic acid has the same configuration as (−)-α-benzylethylamine hydrochloride [from the (+)amine] (Kenyon, Phillips, and Pittman, *J.*, 1935, 1072). Therefore, it appears highly probable that (+)hydratropic acid and (−)-α-phenylethylamine possess similar configurations, and it follows that, during the rearrangements now described, not only is molecular asymmetry retained but molecular configuration as well.*

EXPERIMENTAL.

dl-*Hydratropic acid.* A suspension of sodamide (47 g.) in dry ether was gradually added to a well-stirred solution of redistilled benzyl cyanide (140 g.) in ether (100 c.c.), and the whole heated under reflux for 3 hours. It was then cooled in ice and, during 4 hours, mixed with methyl sulphate (170 g.); after being stirred for 8 hours, at room temperature, water was added and the ethereal layer separated and dried. The α-phenylethyl cyanide thus obtained (115 g.) had b. p. 110—112°/14 mm. This cyanide (100 g.) was added to a mixture of water (88 c.c.), acetic acid (105 c.c.) and conc. sulphuric acid (115 c.c.); refluxing began spontaneously and was maintained by warming for 3—4 hours. The separated upper layer was washed with water, dissolved in 2N NaOH and the alkaline solution extracted with ether and acidified. The resulting hydratropic acid (84 g.) had b. p. 153—155°/20 mm. (+)Hydratropic acid, m. p. 28°, $\alpha_D^{16.5°}$ +51·71° (*l*, 0·5), was obtained as described by Arcus and Kenyon (*loc. cit.*) who give m. p. 29°, $\alpha_D^{16°}$ +51·81° (*l*, 0·5).

* In a recently available publication Brodskii and Mikluklin (*Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **32**, 558) state that when the reaction product of benzophenone oxime hydrochloride and phosphorus pentachloride is decomposed with water enriched with O^{18} the resultant benzanilide contains O^{18}; these authors conclude therefore that the rearrangement is *inter*molecular so far as the migration of oxygen is concerned.

As the Beckmann change involves two migrations of groups (i) a radical from carbon to nitrogen and (ii) –OH (or –OX) from nitrogen to carbon it is perhaps natural to assume that they together constitute a single molecular rearrangement which may be either *intra-* or *inter*-molecular. Consideration of the results of the Russian investigators together with those now described suggests that the migration of R is *intra*molecular whilst that of OX is *inter*molecular, and subsequent to the initial migration.

It is possible, however, to criticise the use of phosphorus pentachloride in this connexion, since the intermediate product must almost certainly be an oxygen-free compound and therefore the resultant benzanilide necessarily contains oxygen derived from the water used in the hydrolysis. The argument would have been more convincing if a reagent had been used capable of esterifying the hydroxyl group instead of displacing it.

It is perhaps relevant to point out that whilst sulphuric acid converted α-phenylethyl methyl ketoxime smoothly into crystalline acet-α-phenylethylamide (as described above), phosphorus pentachloride converted it into a product which on reaction with water yielded no crystalline material.

Conversion of (+)-α-phenylethyl methyl ketoxime into (−)acet-α-phenylethylamide. (+)-α-Phenylethyl methyl ketone. To a cold ethereal solution of methylmagnesium bromide (from Mg, 1·5 g.) powdered anhydrous cadmium chloride (4·5 g.) was slowly added with stirring and the mixture stirred for 2 hours at room temperature. To this solution of dimethylcadmium, cooled to 0°, was added dropwise during 30 minutes, an ethereal solution of (+)-hydratropoyl chloride (from 7·3 g. of acid). The reaction mixture, after being heated under reflux for 3 hours, was decomposed with dilute sulphuric acid and extracted with ether; the ethereal extract was washed with alkali, dried, and distilled yielding (+)-*α-phenylethyl methyl ketone* (5·0 g.), b. p. 116—117°/12 mm., $\alpha_D^{13.7^\circ}$ + 58·21°; $\alpha_D^{14.9^\circ}$ + 58·18°; $\alpha_D^{16.4^\circ}$ + 58·14° (*l*, 0·5) (Found : C, 81·3; H, 8·4. $C_{10}H_{12}O$ requires C, 81·1; H, 8·1%).

(+)-*α-Phenylethyl methyl ketoxime.* The (+)-ketone (5 g.) was added to a solution of hydroxylamine hydrochloride (2·4 g.) and sodium acetate (2·7 g.) in water (15 c.c.) and alcohol (18 c.c.) and the whole heated under reflux for 4 hours. The resulting *oxime* separated from alcohol in needles, m. p. 96° (3·1 g.), $[\alpha]_D^{14.5^\circ}$ +25·4° (*l*, 1; *c*, 2·437, ethanol), $[\alpha]_D^{14.1^\circ}$ + 17·4° (*l*, 1; *c*, 2·031, benzene) (Found : C, 73·7; H, 7·8; N, 8·6. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%).

(−)*Acet-α-phenylethylamide.* Conc. sulphuric acid (2·5 g.) was added dropwise to a stirred solution of the (+)-oxime (2·5 g.) in dry ether (50 c.c.) and the mixture heated under reflux for 30 minutes; after evaporation of the ether and addition of ice, a crystalline precipitate of (−)-acet-α-phenylethylamide (1·4 g.) was obtained having $[\alpha]_D^{15.7^\circ}$ −167·7° (*l*, 2; *c*, 2·177), $[\alpha]_D^{15.2^\circ}$ −167·1° (*l*, 2; *c*, 2·094) both in ethanol. It separated from aqueous acetic acid in plates, m. p. 103—104°, alone and mixed with an authentic specimen, prepared by the action of acetic anhydride on (−)-α-phenylethylamine, which had m. p. 104°, $[\alpha]_D^{17^\circ}$ −168·1° (*l*, 2; *c*, 2·117, ethanol).

Conversion of (+)hydratropic acid into (−)-α-phenylethylamine via *the hydroxamic acid. (+)-Phenylmethylacethydroxamic acid.* A solution of (+)-hydratropoyl chloride (5 g.) in benzene (18 c.c.) was added dropwise to a stirred solution of hydroxylamine (2 g.) in benzene (15 c.c.) at 0°; the separated white solid was collected after some hours and crystallised from ethyl acetate in needles (3·8 g.), m. p. 126°, $[\alpha]_D^{17^\circ}$ +20·3° (*l*, 1; *c*, 2·133, water), $[\alpha]_D^{17^\circ}$ +51·5° (*l*, 1; *c*, 5·132, ethanol), $[\alpha]_D^{17.5^\circ}$ +36·4° (*l*, 1; *c*, 2·173 acetone) (Found : N, 8·4. $C_9H_{11}O_2N$ requires N, 8·5%). It gave a cherry-red colouration with aqueous ferric chloride.

The corresponding *dl*-hydroxamic acid, prepared by the same method, had m. p. 119—120° (Found : N, 8·7%).

(+)*Benzoyl phenylmethylacethydroxamate.* Benzoyl chloride (3·5 c.c.) was added in several portions with vigorous shaking to a cold solution of the (+)-hydroxamic acid (3·8 g.) in acetic acid (25 c.c.) and a saturated aqueous solution of sodium acetate (25 c.c.). The precipitated solid was separated, washed with water, and dried under reduced pressure. It separated from ethyl acetate–ligroin in plates (3·5 g.), m. p. 153°, $[\alpha]_D^{17^\circ}$ +39·4° (*l*, 1; *c*, 3·279, alcohol), $[\alpha]_D^{15^\circ}$ +22·3° (*l*, 1; *c*, 2·785, chloroform), $[\alpha]_D^{15}$ +28·6° (*l*, 1; *c*, 2·906, benzene) (Found : N, 5·1. $C_{16}H_{15}O_3N$ requires N, 5·2%).

The corresponding *dl*-benzoyl derivative, prepared by the same method, had m. p. 148° (Found: N, 5·2%).

Potassium benzoyl phenylmethylacetylhydroxamate. A solution of potassium (0·83 g.) in anhydrous methanol (8 c.c.) was added to a solution of the (+)-benzoyl derivative (3·5 g.) in warm acetone (50 c.c.) and the potassium derivative separated as a colourless microcrystalline powder. Anhydrous ether (30 c.c.) was added and the solid (3·7 g.) separated by filtration.

(−)-*α-Phenylethylamine.* The potassium salt (3·7 g.) was mixed with dry benzene (25 c.c.) and heated under reflux for an hour; the suspension was then filtered to remove potassium benzoate. The filtrate * was mixed with conc. hydrochloric acid (5 c.c.), warmed to 45°, and stirred for one hour. After some hours, the aqueous acid layer was separated and rendered alkaline. The liberated (−)-α-phenylethylamine (1·8 g.) had b. p. 72°/12 mm., $[\alpha]_D^{15.6^\circ}$ −18·96° (*l*, 0·5). Its acetyl derivative had m. p. 103—104°, alone or mixed with an authentic specimen, and $[\alpha]_D^{18^\circ}$ −166·9° (*l*, 2; *c*, 2·209) in ethanol.

Conversion of (+)-hydratropic acid into (−)-α-phenylethylamine via *hydratropic azide* (*Schmidt rearrangement*). Sulphuric acid (10 c.c.) was added to a solution of (+)hydratropic acid (5 g.) in chloroform (40 c.c.); sodium azide (4 g., 1·2 mols.) was then added slowly to the vigorously stirred solution maintained at 45°. After 30 mins., the evolution of nitrogen having ceased, the solution was rendered alkaline and extracted with ether. The resulting (−)-α-phenylethylamine (2·9 g.) had $[\alpha]_D^{14.3}$ −19·04° (*l*, 0·5); by the action of acetic anhydride it was converted into (−)acet-α-phenylethylamide, leaflets from aqueous acetic acid, m. p. 103—104°, alone or when mixed with an authentic specimen, $[\alpha]_D^{17^\circ}$ −165·2° (*l* 2; *c*, 2·499, ethanol).

A parallel experiment, using hydratropic acid having $[\alpha]_D^{11.5^\circ}$ +32·47° (*l*, 0·5), yielded α-phenylethylamine having $[\alpha]_D^{14.2^\circ}$ −11·80° (*l*, 0·5). The optical purity of the acid was 62·1% and of the amine 61·7%; thus, the retention of optical activity was 99·4%.

It was shown by Bernstein and Whitmore (*J. Amer. Chem. Soc.*, 1939, **61**, 1324) that the azide of incompletely resolved (+)hydratropic acid, having $[\alpha]_D^{25.5^\circ}$ +86·1°, was converted by the Curtius reaction into α-phenylethylamine, the benzoyl derivative of which had $[\alpha]_D^{27^\circ}$ −39·2° in benzene; reference to this result ought to have been made in the paper by Kenyon and Young (*loc. cit.*), but these authors much regret they were unaware of it at the time.

The benzoyl derivative of the (−)-α-phenylethylamine obtained by the first Schmidt rearrangement described above had $[\alpha]_D^{16^\circ}$ −41·8° (*l*, 2; *c*, 2·634, benzene) and $[\alpha]_D^{16.5^\circ}$ −149° (*l*, 0·5; *c*, 1·167, carbon disulphide).

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