194. *The Mechanism of the Hofmann Reaction. Retention of Optical Activity during the Reaction with (+)Hydratropamide.*

By C. L. Arcus and J. Kenyon.

The Hofmann rearrangement of (+)hydratropamide into (−)-α-phenylethylamine has been examined. This reaction provides a favourable case for observing whether any dissociation of the amide molecule occurs during the Hofmann rearrangement, since the electron-releasing properties of the α-phenylethyl radical should favour this dissociation with subsequent racemisation of the liberated radical, while the comparatively high rotatory power of (−)-α-phenylethylamine would facilitate the detection of racemisation.

It is found that optical activity is almost completely retained during the rearrangement of (+)hydratropamide, in confirmation of the conclusions of previous workers that the Hofmann rearrangement is substantially an intramolecular reaction. A formulation of the rearrangement is suggested.

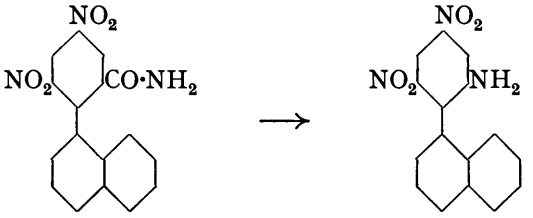
It appears to be established that the Hofmann reaction of amides proceeds by the following stages :

$$R{\cdot}CO{\cdot}NH_2 \xrightarrow{Br_2} R{\cdot}CO{\cdot}NHBr \xrightarrow{NaOH} (Salt) \longrightarrow NR{:}C{:}O + NaBr \longrightarrow R{\cdot}NH_2$$

the molecular rearrangement, in which the group R becomes detached from the carbon and attached to the nitrogen atom, being confined to the third stage of the process.

The following evidence indicates the rearrangement to be intramolecular rather than one which involves dissociation of the molecule into free ions or radicals. Whitmore and Homeyer (*J. Amer. Chem. Soc.*, 1932, **54**, 3435) have observed that *tert.*-butylacetamide yields *neo*pentylamine quantitatively: $CMe_3{\cdot}CH_2{\cdot}CO{\cdot}NH_2 \longrightarrow CMe_3{\cdot}CH_2{\cdot}NH_2$, whereas those reactions in which the temporary existence of the cation $CMe_3{\cdot}\overset{\oplus}{C}H_2$ may occur lead to *tert.*-amyl derivatives, *e.g.*, $CMe_3{\cdot}CH_2I + NaOAc \longrightarrow CMe_2Et{\cdot}OAc + NaI$.

On performing the Hofmann reaction with (+)benzylmethylacetamide, Wallis and Nagel (*ibid.*, 1931, **53**, 2787) obtained α-benzylethylamine in apparent optical purity; further, Wallis and Moyer (*ibid.*, 1933, **55**, 2598) submitted an optically active compound of the diphenyl type to the Hofmann reaction, again obtaining an apparently optically pure amine :



Dissociation of the diphenyl radical from the amido-group at any stage of the reaction would have permitted free rotation and resulted in a racemic product. It may be pointed out that in neither of the last two cases was a direct evaluation of the optical purity of the resultant amine made by comparison of its rotatory power with that of the active amine prepared by resolution of the *dl*-compound.

(+)Hydratropamide, $CHMePh{\cdot}CO{\cdot}NH_2$, has now been prepared and submitted to the Hofmann reaction; this particular amide was selected for the following reasons. The resultant α-phenylethylamine has been resolved by numerous workers (references given in " Organic Syntheses," Vol. XVII, 80); moreover, the radical $CHMePh{\cdot}$ would be expected to exhibit a stronger tendency towards electron release than the radicals $CH_2Ph{\cdot}CHMe{\cdot}$ and $C_{10}H_7{\cdot}C_6H_2(NO_2)_2{\cdot}$, so that if rearrangement by dissociation of the

amide molecule, with consequent racemisation, can occur, it would be more evident in the case of the rearrangement of hydratropamide than in the cases which have previously been reported. From a study of the rearrangement of (—)phenylmethylcarbinyl *p*-toluenesulphinate into *dl*-α-phenylethyl-*p*-tolylsulphone (Arcus, Balfe, and Kenyon, J., 1938, 485) it was concluded that the reaction

$$(-)\text{CHMePh}\cdot\text{O}\cdot\text{SO}\cdot\text{C}_7\text{H}_7 \longrightarrow dl\text{-CHMePh}\cdot\text{SO}_2\cdot\text{C}_7\text{H}_7$$

involves the liberation of the cation $\text{CHMePh}^{\oplus}$; dissociation into this cation, which is planar, is favoured by the use of hydroxylic solvents of high dielectric constant. It was therefore considered that, should dissociation occur during the Hofmann reaction, hydratropamide would provide a favourable example for its detection. Finally, as the rotatory powers of both hydratropic acid and α-phenylethylamine are of considerable magnitude, any racemisation which occurs during the reaction can be estimated with some degree of accuracy.

dl-Hydratropic acid was prepared as described in the experimental section, and by fractional crystallisation of its strychnine salt as described by Raper (J., 1923, **123**, 2557) optically pure (+)hydratropic acid was obtained. A method is described for the preparation of (—)hydratropic acid also.

(+)*Hydratropamide*, prepared through the acid chloride, was treated with a solution of bromine in sodium hydroxide and (—)-α-phenylethylamine obtained. The optical rotatory power of the latter was determined (after extraction and distillation, processes which are unlikely to effect any change in the optical purity of the product) and compared with the value $\alpha_{5461}^{16\cdot5^\circ}$ —22·92° (*l*, 0·5), the highest in the literature, obtained by Ingold and Wilson (J., 1933, 1503) who resolved the *dl*-base with *d*-bromocamphorsulphonic acid. Four separate experiments were carried out with the following results :

Observed Rotatory Powers of Hydratropic Acid and of α-Phenylethylamine obtained from it (l, 0·5).

	Hydratropic acid.	Optical purity, %.	α-Phenylethylamine.	Optical purity, %.	Retention of optical activity, %.
(i)	$\alpha_{5461}^{16^\circ}$ +62·18°	100	$\alpha_{5461}^{15^\circ}$ —21·81°	95·1	95·1
(ii)	$\alpha_{5461}^{16\cdot8^\circ}$ +62·07	100	$\alpha_{5461}^{16^\circ}$ —21·92	95·6	95·6
(iii)	$\alpha_{5461}^{19^\circ}$ +55·22	90·0	$\alpha_{5461}^{17^\circ}$ —19·65	85·8	95·3
(iv)	$\alpha_{5461}^{18^\circ}$ —15·85	25·8	$\alpha_{5461}^{17^\circ}$ + 5·75	25·1	97·2
					Mean 95·8

It is seen that asymmetry is almost completely retained during the rearrangement. The mechanism of rearrangement during the Hofmann reaction has been represented in two ways. Stieglitz and also Wallis (review on molecular rearrangements by Wallis, " Organic Chemistry," Gilman, Vol. I, 1938, 720) postulate the formation of a univalent nitrogen compound :

$$\text{R}\cdot\text{CO}\cdot\text{NHBr} \longrightarrow \text{R}\cdot\text{CO}\cdot\text{N}\!<\!\longrightarrow \text{R}\cdot\text{N}{:}\text{C}{:}\text{O}$$

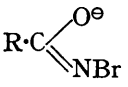
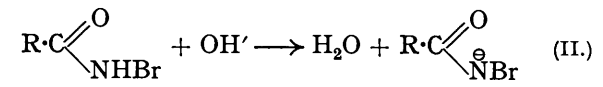
The rearrangement has also been formulated as analogous to the Beckmann rearrangement (Franklin, *Chem. Reviews*, 1934, **14**, 219; Sidgwick, " Organic Chemistry of Nitrogen," 1937, p. 146) :

$$\text{R}\!-\!\underset{\underset{\text{N}\!-\!\text{Br}}{\|}}{\text{C}}\!-\!\text{O}^{\ominus} \longrightarrow \text{Br}\!-\!\underset{\underset{\text{N}\!-\!\text{R}}{\|}}{\text{C}}\!-\!\text{O}^{\ominus} \longrightarrow \text{R}\cdot\text{N}{:}\text{C}{:}\text{O} + \text{NaBr}$$

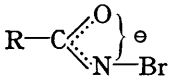
There appears to be no evidence that the bromine atom is at any time attached to the carbonyl carbon atom; however, this representation indicates that if the movements of R– and Br– are simultaneous, it is unnecessary to postulate the existence of a univalent nitrogen atom.

It was shown by Hantzsch (*Ber.*, 1902, **35**, 226, 3579) that the bromo-amide forms a

salt by interaction with the alkali, the anion of which was formulated as in (I). If it is assumed that the initial salt-forming reaction is

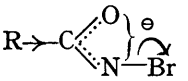
(I.)   (II.)

then (I) and (II) should undergo resonance, and the anion and its rearrangement may be represented by

(III.) 

expulsion of the bromine anion and movement of the group R– being simultaneous.

A tendency to electron release by R (+ *I* effect) will promote the liberation of $Br^{\ominus}$ and increase the ease of rearrangement :



This is in accordance with the observation of Hauser and Renfrow (*J. Amer. Chem. Soc.*, 1937, **59**, 121) that the rates of decomposition (by sodium hydroxide at 30°) of a number of *p*- and *m*-substituted *N*-bromobenzamides increase as the dissociation constants of the corresponding benzoic acids decrease.

A secondary effect may be observed when R is a semiaromatic group; attachment of aromatic nuclei should weaken the R–C bond [analogously to the formation of free radicals by dissociation of $C(Ar)_3$–X] and thereby promote rearrangement. This has been observed by Jones and Hurd (*ibid.*, 1921, **43**, 2422) in the closely related hydroxamic acid rearrangement,

$$R{\cdot}CO{\cdot}NH{\cdot}OH \longrightarrow R{\cdot}N{:}C{:}O + H_2O$$

where the ease of rearrangement increases as R– is successively $-CH_2Ph$, $-CHPh_2$, and $-CPh_3$.

Since very little racemisation was observed in the above reaction with (+)hydratropamide, it appears certain that the group R– does not migrate as an ion or free radical [it is also very improbable that the anion (III) would further dissociate into a carbonium cation], but that the electronic changes during the movement of R– are such that electronic sharing between R– and the structure $C<_{N-}$ is continuous.

It may be noted that the Hofmann reaction should be a reliable procedure in the determination of the relative configurations of compounds of the type $Cabc{\cdot}CO_2H$ and $Cabc{\cdot}NH_2$, as has been suggested by Braun and Friehmelt (*Ber.*, 1933, **66**, 684).

Experimental.

dl-Hydratropic acid was prepared, in larger amounts, by oxidation (by far the most conveniently, with potassium permanganate and magnesium sulphate in aqueous acetone solution) of hydratropaldehyde obtained by a modification of methods due to Tiffeneau (*Ann. Chim. Phys.*, 1907, **10**, 176), Klages (*Ber.*, 1905, **38**, 1969), and Cohen, Woodman, and Marshall (J., 1915, **107**, 898) based on the reactions :

$$COMe{\cdot}CH_2Cl \xrightarrow{PhMgBr} CMePh(OH){\cdot}CH_2Cl \xrightarrow{NaOEt} CMePh{\cdot}CH_2 \xrightarrow{HCl} CHMePh{\cdot}CHO.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

(+)*Hydratropic Acid.*—A solution of strychnine (90 g.) and *dl*-hydratropic acid (40 g.) in warm 75% aqueous alcohol (400 c.c.), after standing overnight in the ice-chest, deposited 60 g. of strychnine salt in the form of glassy rhombs; concentration of the filtrate yielded a second crop (25 g.). After five recrystallisations, optical purity was reached, and the strychnine salt yielded *d*-hydratropic acid (8·5 g.), b. p. 143°/12 mm., which sets to a mass of transparent, flat rhombs, m. p. 29° : in view of its considerable alteration of rotatory power with change of temperature, the following values were determined (*l*, 0·5).

$t.$	α_{5893}.	α_{5780}.	α_{5461}.	α_{4358}.	$t.$	α_{5780}.	α_{5461}.	α_{4358}.
13·6°	—	+55·04°	+63·08°	+112·5°	23°	+53·03°	+60·73°	+109°
16·0	+51·81°	—	62·16	111·2	25	52·30	59·80	108
16·2	—	54·30	62·30	111·7	30	51·30	·58·62	105·7
17·75	—	—	61·85	—				
19·4	—	53·55	61·30	110				

Specific rotatory powers of the acid in solution are given below.

Collected Specific Rotatory Powers.

Solute.	Solvent.	$c.$	$l.$	$[\alpha]_{5893}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.
d-Hydratropic acid *	$CHCl_3$	3·060	2	+ 74·8°	+ 90·9°	+162°
,, ,,	C_6H_6	3·4825	2	92·5	110·3	197
,, ,, (Na salt)	H_2O	3·247	2	5·8	6·3	9·2
d-Hydratropamide	$CHCl_3$	2·733	2	58·3	71·5	130
d-α-Phenylethylacetamide	EtOH	2·340	2	−165	−195	−370

* *d*-Configuration is assigned arbitrarily to (+)hydratropic acid for the purpose of description.

(−)*Hydratropic Acid.*—From the first mother-liquor from the strychnine salt there was recovered hydratropic acid (12 g.) with $\alpha^{19°}_{5893}$ −32·28° (*l*, 0·5), which, on being kept in the ice-chest for several days, deposited a crop of crystals; the liquid acid drained from the crystals had $\alpha^{19°}_{5893}$ −26·6° (*l*, 0·5). The crystals were melted, allowed to recrystallise, and again drained from the liquid acid. When the process was repeated a third time there was obtained (−)hydratropic acid (4 g.) in hard, glassy, flat rhombs, m. p. 29°, and (supercooled) $\alpha^{17°}_{5461}$ −61·68° (*l*, 0·5).

In view of the readiness with which this separation takes place the—presumed—optically pure (+)hydratropic acid described above was melted, inoculated, and when crystallisation was about two-thirds complete, the liquid portion was drained away. The rotatory power of the re-melted acid was identical with that of the original acid, thus increasing very considerably the probability that optical purity had been reached by the fractional crystallisation of strychnine hydratropate.

This is the more desirable because Levene and Marker (*J. Biol. Chem.*, 1933, **100**, 692), who fractionally crystallised its quinine salt, give $[\alpha]^{25°}_{5893}$ −74·1° as the maximum value of *l*-hydratropic acid in the homogeneous condition, whereas Ott and Krämer (*Ber.*, 1935, **68**, 1657) state, without recording any experimental details, that optically pure *d*-hydratropic acid has $[\alpha]^{20°}_{5893}$ + 89·7°. Also, during the present investigation it was found that lævorotatory hydratropic acid with $\alpha^{19°}_{5893}$ − 27·1° (*l*, 0·5) gives a beautifully crystalline cinchonidine salt which was recrystallised successively from acetone, methyl acetate (twice), and aqueous alcohol without the rotatory power of the liberated hydratropic acid being increased beyond $\alpha^{19°}_{5893}$ − 36° (*l*, 0·5). On the other hand, Raper (*loc. cit.*), whose method we have used, gives for the *d*-acid $[\alpha]_{5893}$ + 76·2° in chloroform solution, but records no value for the homogeneous acid, owing to the small amount available.

Even in this most favourable case we found it advantageous to allow the crystallisation to proceed undisturbed and to decant the mother-liquor; when the containing vessel is scratched, a considerable amount of strychnine salt of low optical activity is brought out of solution.

An attempt was made to obtain *l*-hydratropic acid by the recrystallisation from ether of *l* + *dl*-hydratropamide (from hydratropic acid of $\alpha^{19°}_{5893}$ − 25·5°, *l* 0·5), but after three crystallisations the resulting amide had only $[\alpha]_{5461}$ − 43·9° in chloroform solution.

A crystal of *d*-hydratropic acid was at room temperature placed in contact with a similar crystal of *l*-hydratropic acid: they slowly melted and the resulting *dl*-acid remained liquid after being kept at − 5° for several days.

(+)*Hydratropamide* was prepared by warming a mixture of (+)hydratropic acid (7·5 g.) and phosphorus trichloride (2·8 g.) at 60—70° for an hour and pouring the upper mobile layer of hydratropyl chloride dropwise into ammonia (25 c.c.; *d* 0·880) at −18°. The precipitated crystalline hydratropamide was removed by filtration, washed with cold water, and air-dried; it (7·2 g.) had m. p. 96—97° and rotatory powers given above. It separated from warm water, in which it was but sparingly soluble, in slender, long needles, or from chloroform–light petroleum in lustrous leaflets, m. p. 103—104° (Found: N, 8·9. $C_9H_{11}ON$ requires N, 9·4%).

(−)-α-*Phenylethylamine.*—The (+)hydratropamide (6·8 g., uncrystallised so as to avoid any possible separation of optical isomerides) was gradually added to a cooled solution of sodium hydroxide (8 g.) and bromine (8·3 g.) in water (50 c.c.). The resulting cloudy solution was gently heated on the steam-bath for 20 minutes until separation of the amine appeared to be

complete. Extraction with ether yielded (—)-α-phenylethylamine (3·5 c.c.), b. p. 73°/14 mm., $\alpha_{5893}^{15°|}$ — 18·20°, $\alpha_{5461}^{15°|}$ — 21·81°, $\alpha_{4358}^{15°}$ — 37·3° (*l*, 0·5), $d_{4°}^{17·5°}$ 0·9762, $d_{4°}^{25°}$ 0·9702, $d_{4°}^{31°}$ 0·9650.

(—)-α-Phenylethylacetamide, prepared by the action of acetic anhydride on the (—)amine, separated from aqueous acetic acid in leaflets, m. p. 103—104°, and had the rotatory powers given above. Götze (*Ber.*, 1938, **71**, 2289), who prepared the acetyl derivative of (—)-α-phenylethylamine with $[\alpha]_{5893}$ — 33°, gives m. p. 101—102° and $[\alpha]_{5893}$ — 170° in ethyl-alcoholic solution.

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