398. *The Hofmann Reaction with α- and β-Hydroxy-amides: Reactions of the Intermediate* iso*Cyanates.*

By C. L. Arcus and D. B. Greenwood.

A mechanism for the (Weerman) degradation of an α-hydroxy-amide R·CH(OH)·CO·NH_2 is proposed in which the aldehyde R·CHO is formed by the elimination of cyanate ion from the intermediate anion $^-$O·CHR·NCO.

Methyl *N*-1-methoxyethylcarbamate has been prepared; its acidic hydrolysis yields acetaldehyde, carbon dioxide, and ammonia, but not methylamine.

Salicylamide with hypochlorite in strongly alkaline solution yields 4 : 5-benzoxazol-2-one (Graebe and Rostovzeff, *Ber.*, 1902, **35**, 2747), but in less basic solutions 5- and 3-chloro-2-hydroxybenzamides are formed; the mechanism of the reaction is discussed.

β-Hydroxy-β-phenylpropionamide with bromine and methanolic sodium methoxide yields 5-phenyloxazolid-2-one.

The main characteristics of the Hofmann reaction with different types of hydroxy-amide are already known, but the mechanisms of a number of reactions within this field have not been fully elucidated; several such reactions have now been investigated.

It has been established (Ault, Haworth, and Hirst, *J.*, 1934, 1722; Haworth, Peat, and Whetstone, *J.*, 1938, 1975) that the reaction of aqueous hypochlorite and alkali with an α-hydroxy-amide yields the aldehyde together with the cyanate ion (1), and that a similar reaction with an α-methoxy-amide yields the aldehyde and ammonia, but no cyanate (2). Ault *et al.* consider that in (2) the hydrolysis of the *iso*cyanate proceeds *via*

$$\text{R·CH(OH)·CO·NH}_2 \xrightarrow{\text{NaOCl}} \text{R·CH(OH)·NCO} \xrightarrow{\text{NaOH}} \text{R·CHO} + \text{NaCNO} \quad . \quad . \quad (1)$$

$$\text{R·CH(OMe)·CO·NH}_2 \xrightarrow{\text{NaOCl}} \text{R·CH(OMe)·NCO} \xrightarrow{\text{NaOH}} \text{R·CHO} + \text{MeOH} + \text{Na}_2\text{CO}_3 + \text{NH}_3 \quad . \quad (2)$$

the carbamate (I; R′ = Na), a conclusion supported by the observation that benzaldehyde and ammonia are formed quantitatively by alkaline hydrolysis of methyl *N*-α-methoxybenzylcarbamate (I; R = Ph, R′ = Me). These authors suggest that in (1) "the formation of a co-ordinated intermediate product (II), in place of a carbamic acid, is responsible for the marked difference in the character of the end products." It is now

$$\underset{\text{(I)}}{\text{R·CH(OMe)·NH·CO}_2\text{R′}} \qquad \underset{\text{(II)}}{\text{R·CH(OH)·NCO}}$$

suggested that (1) proceeds by an elimination mechanism: the electron-attracting *iso*cyanate group renders the hydroxyl-hydrogen atom weakly acidic, and the anion (III) is formed either by direct ionisation or by the attack of a hydroxyl ion, electronic movements as shown then yielding the aldehyde and cyanate ion:

$$\text{HO}^- + \text{R·CH(OH)·N:C·O} \longrightarrow \underset{\text{(III)}}{\text{R·CH(O}^-\text{)·N:C·O}} + \text{H}_2\text{O} \longrightarrow \text{R·CHO} + \text{NCO}^-$$

Methylation of the hydroxyl group renders this process impossible, in accordance with the experimental finding.

Haworth *et al.* (*loc. cit.*), following earlier work by Irvine and Pryde (*J.*, 1924, **125**, 1045) and Humphreys, Pryde, and Waters (*J.*, 1931, 1298), isolated the cyclic urethanes (IV; $m = n = 2$; and $m = 1$, $n = 3$) from the reaction of aqueous hypochlorite with

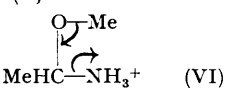
2 : 3 : 5 : 6- and 2 : 3 : 4 : 6-tetramethylgluconamide; these compounds respectively contain a 6- and a 7-membered ring formed by intramolecular reaction between a hydroxyl and an *iso*cyanate group. The reaction with 3 : 5 : 6-trimethylgluconamide, which bears hydroxyl groups at $C_{(2)}$ and $C_{(4)}$, yielded 2 : 4 : 5-trimethylarabinose and cyanate; no cyclic urethane could be isolated. It is inferred from this result that elimination *via* (III) is more rapid than urethane formation.

$$H\cdot[CH(OMe)]_m\cdot\overset{\overset{\Large O}{\frown}}{CH}\cdot[CH(OMe)]_n\cdot NH\cdot CO \quad \text{(IV)}$$

Methyl *N*-1-methoxyethylcarbamate (I; R = R′ = Me) has been prepared by the reaction of α-methoxypropionamide with bromine and methanolic sodium methoxide. Acidic hydrolysis of this carbamate yielded acetaldehyde, and nearly the theoretical quantities of carbon dioxide and ammonia; methylamine was absent. The following course for the hydrolysis appears to be the most probable. The amido-link is first hydrolysed :

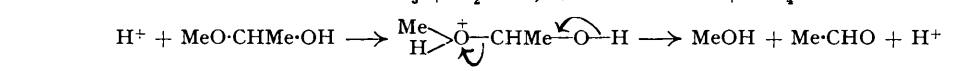
$$MeO\cdot CHMe\cdot NH\cdot CO_2Me + H^+ + H_2O \longrightarrow MeO\cdot CHMe\cdot \overset{+}{N}H_3 + MeHCO_3$$
(V)

$$MeHCO_3 \longrightarrow MeOH + CO_2$$


(VI)

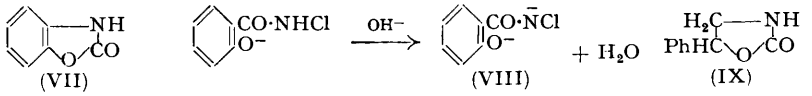
Since methylamine is not a product of the reaction the ion (V) does not react as in (VI), and further hydrolysis occurs :

$$MeO\cdot CHMe\cdot \overset{+}{N}H_3 + H_2O \longrightarrow MeO\cdot CHMe\cdot OH + NH_4^+$$



Graebe and Rostovzeff (*Ber.*, 1902, **35**, 2747), by the action of sodium hypochlorite (2 mols.) and sodium hydroxide (4·5 mols.) on salicylamide, obtained 4 : 5-benzoxazol-2-one (VII); this preparation has been repeated. Further, it has been found that the interaction of equimolar quantities of hypochlorite and salicylamide yields 5- and 3-chloro-2-hydroxybenzamides; no (VII) was isolated. Reaction in the presence of two mols. of alkali gave a similar result. It is concluded that the anion of the *N*-chloroamide (VIII), the essential precursor to the Hofmann rearrangement, is formed only when the hydroxyl-ion concentration is high, electron-release from the existing phenoxide ion opposing the removal of a second proton. The Hofmann reaction is therefore inhibited in solutions which are not strongly alkaline, and substitution (by hypochlorous acid, hypochlorite ion, or chloramine) then occurs in the nucleus.

Reaction of β-hydroxy-β-phenylpropionamide with bromine and methanolic sodium methoxide yielded the 5-membered cyclic urethane, 5-phenyloxazolid-2-one (IX), a result analogous to the formation of (VII) and of the 6- and 7-membered cyclic urethanes (IV; $m = n = 2$) and (IV; $m = 1, n = 3$).


(VII) (VIII) (IX)

Experimental

Amides were prepared by the reaction of esters with ammonia under the conditions described in the first preparation.

Ethyl α-methoxypropionate (51 g.; Nieman, Benson, and Read, *J. Org. Chem.*, 1943, **8**, 397) and ammonia (*d* 0·88; 300 ml.) were shaken mechanically in a stoppered bottle; when the mixture had become homogeneous it was kept for 10 days and then evaporated under reduced pressure. The distilled product, b. p. 111°/18 mm., was recrystallised from benzene–*cyclo*hexane and yielded α-methoxypropionamide (42 g.), m. p. 81° (Found, by hydrolysis with aqueous-alcoholic 0·5N-potassium hydroxide : equiv., 101. Calc. for $C_4H_9O_2N$: equiv., 103). Gauthier (*Ann. Chim.*, 1909, **16**, 315) records m. p. 81°.

Ethyl salicylate (70 g.), with ammonia (400 ml.) and ethanol (60 g.) for 6 days, yielded salicylamide (54 g., from benzene–acetone), m. p. 137°.

Ethyl β-hydroxy-β-phenylpropionate (10·5 g.; Hauser and Breslow, *Org. Synth.*, 1941, **21**, 51), with ammonia (150 ml.) for 2 days, yielded β-hydroxy-β-phenylpropionamide (8·9 g., from chloroform–ethanol), m. p. 122—123°. Posner (*Ber.*, 1905, **38**, 1129) records m. p. 122—123°.

Methyl N-1-*Methoxyethylcarbamate.*—Sodium (4·7 g.) was allowed to react with dry methanol (100 ml.) and to the solution, cooled in ice, was added α-methoxypropionamide (10·3 g.) in methanol (30 ml.); bromine (16·3 g.) was added dropwise with stirring, the mixture being kept below 2°. It was then heated under reflux for 15 min., cooled, and made neutral to phenolphthalein with glacial acetic acid, and the methanol distilled off through a short column; the residue was extracted with ether. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated. The product on distillation yielded *methyl* N-1-*methoxyethylcarbamate* (7·3 g.), b. p. 77°/16 mm., n_D^{25} 1·4241 (Found: C, 45·4; H, 8·2; N, 10·2. $C_5H_{11}O_3N$ requires C, 45·1; H, 8·3; N, 10·5%).

Hydrolyses. Methyl *N*-1-methoxyethylcarbamate (1·5 g.) was weighed into a flask which was then connected to two traps, the first cooled in ice, the second with solid carbon dioxide. The second trap was connected to a calcium chloride-filled U-tube which had been saturated with carbon dioxide and purged with hydrogen, a weighed U-tube the first two-thirds of which were filled with soda-lime and the last third with calcium chloride, and finally to a soda-lime guard tube. 4N-Sulphuric acid (40 ml.) was run into the flask which was then heated with steam. Carbon dioxide-free hydrogen was passed through the apparatus during the hydrolysis, which was allowed to proceed for 4 hr., by which time the weight of the central tube (after it had been purged with carbon dioxide-free air) had become constant. In a control experiment with sodium hydrogen carbonate, 98% of the theoretical quantity of carbon dioxide was collected. An aliquot of the hydrolysis solution (which gave no carbylamine with chloroform and alkali) was used for a Kjeldahl determination of ammonia. The following tests were applied to the ammonium chloride obtained on evaporation: (*a*) it was insoluble in hot absolute alcohol; (*b*) the filtrate from extraction with 96% alcohol gave no colour with 2 : 4-dinitrochlorobenzene, or when warmed to 75° with tetrachloroquinone. Methylamine was therefore absent. From the contents of the traps there was prepared a semicarbazone having m. p. 160° alone and when mixed with authentic acetaldehyde semicarbazone of m. p. 161—162°, and a dimedone derivative having m. p. 139° alone and when mixed with authentic acetaldehyde–dimedone compound having m. p. 139°. There were obtained carbon dioxide (i) 105, (ii) 100%, and ammonia (i) 94, (ii) 96% of the theoretical quantities.

The hydrolysis of methyl *N*-1-methoxyethylcarbamate (2·66 g.) with 1·5N-sodium hydroxide (200 ml.) for 1½ hr. at 50° and finally at 95° (the absorption tubes were omitted) yielded a tar (0·46 g.) and, in the colder trap, a solid which decomposed at 70° to ammonia and acetaldehyde; these products were presumed to be, respectively, acetaldehyde resin and acetaldehyde-ammonia. A portion of the hydrolysis solution was treated with pyridine, sufficient acetic acid to render the mixture acid, chloroform, and 1% aqueous copper sulphate: the chloroform layer developed no blue colour, whence cyanate was absent.

Salicylamide–Hypochlorite Reactions.—(*a*) Salicylamide (3·0 g.) yielded, by Graebe and Rostovzeff's method (*loc. cit.*), a product, the benzene solution of which was heated with charcoal at 65° for 1 hr.; on cooling there separated 4 : 5-benzoxazol-2-one (1·0 g.), colourless crystals, m. p. 140—141° (these authors record m. p. 138—139°). Admixture with salicylamide depressed the m. p. by 40°.

(*b*) A solution of salicylamide (16·4 g.) in water (50 ml.) was cooled to 0°, 0·92M-sodium hypochlorite (130 ml.) was added with stirring during ¾ hr., and the mixture was heated on a steam-bath for ¾ hr. Next day the solution was saturated with carbon dioxide, which precipitated amides (13·9 g.); acidification with hydrochloric acid yielded a precipitate (2·0 g.) which after recrystallisation from water had m. p. 157° alone and when mixed with salicylic acid. The amides were fractionally crystallised from aqueous dioxan and yielded 5-chloro-2-hydroxybenzamide (3·5 g.), m. p. 227—228° (Found: C, 49·2; H, 3·5; N, 8·0; Cl, 20·4. Calc. for $C_7H_6O_2NCl$: C, 49·0; H, 3·5; N, 8·2; Cl, 20·7%) (Biltz and Stepf, *Ber.*, 1904, **37**, 4024, record m. p. 226—227°), and 3-chloro-2-hydroxybenzamide (7·5 g.), m. p. 183—184° (Found: C, 49·0; H, 3·7; N, 7·9; Cl, 20·1%) (Hirwe, Rana, and Gavankar, *Proc. Indian Acad. Sci.*, 1938, **8**, *A*, 208, record m. p. 174—175°).

(*c*) Salicylamide (2·0 g.), 0·87M-sodium hypochlorite (18 ml.), and 0·88N-sodium hydroxide (34 ml.) were allowed to react as in (*b*). The solution was then progressively acidified with hydrochloric acid, and material which separated was removed, as follows: to pH 8·5, a

precipitate which after recrystallisation from benzene–dioxan had m. p. 225—227° alone and m. p. 226—227° when mixed with 5-chloro-2-hydroxybenzamide from (*b*); to pH 6·8, material m. p. 170—194°; to pH 2, an oil of b. p. approx. 240°, which solidified and appeared to be chlorophenol(s).

5-*Phenyloxazolid*-2-*one*.—Bromine (4·2 g.) was allowed to react with β-hydroxy-β-phenylpropionamide (4·1 g.) and methanolic sodium methoxide (from 1·2 g. of sodium and 150 ml. of methanol) by the procedure used for the preparation of methyl *N*-1-methoxyethylcarbamate; the mixture was heated under reflux for ¾ hr. and then made neutral to phenolphthalein with glacial acetic acid, and the greater part of the methanol was distilled off. Ether was added to the residue, the precipitated sodium bromide was filtered off, and the solvents were distilled; the product, after warming in aqueous solution with charcoal and recrystallisation from water, yielded 5-*phenyloxazolid*-2-*one* (2·0 g.), m. p. 89—90° (Found: C, 65·8; H, 5·5; N, 8·7. $C_9H_9O_2N$ requires C, 66·2; H, 5·6; N, 8·6%). Schroeter (D.R.-P. 220,852) who prepared this compound by heating β-hydroxy-β-phenylpropionyl azide, records m. p. 87—88·5°, but no analysis. 5-Phenyloxazolid-2-one (0·28 g.) was heated on a steam-bath for 1½ hr. with 4N-sodium hydroxide (3 ml.); drops of oil separated. To the cold mixture, benzoyl chloride (0·25 g.) was added with shaking. The product was next day filtered off and after recrystallisation from aqueous alcohol yielded 2-benzamido-1-phenylethanol (0·26 g.), m. p. 147·5—148·5°. Rosenmund (*Ber.*, 1913, **46**, 1046) and Wolfheim (*Ber.*, 1914, **47**, 1440) record m. p. 147° and 148—149·5° respectively.

Thanks are expressed to the University of London and to Imperial Chemical Industries Limited for grants.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, March 10th*, 1953.]