213. *Amides. Part I. Preparation of Diacetimide.*

By J. B. Polya and P. L. Tardrew.

The yield of diacetimide from acetamide and acetic anhydride is improved by dry hydrogen chloride, acetamide hydrochloride, or bisacetamide hydrochloride. Variation of the hydrogen chloride concentration between wide limits has little effect on the yield. The reaction between acetamide and acetic anhydride may proceed by two simultaneous mechanisms.

This investigation was undertaken as part of more extensive studies of the chemistry and biochemistry of amides. Previously described syntheses of diacetimide have the disadvantage of inconvenient operations and low yields. Diacetimide may be prepared by eliminating ammonia from two molecules of acetamide (Strecker, *Annalen*, 1857, **103**, 321; Rakshit, *J.*, 1913, **103**, 1557), by acetylating acetamide (Lindemann, *Sitz. Akad. Wiss. Wien*, Math.-natw. Kl., 1869, **60**, II. Abt., 53; Franchimont, *Rec. Trav. chim.*, 1883, **2**, 344; Hentschel, *Ber.*, 1890, **23**, 2394; Titherley, *J.*, 1901, **79**, 391, 411; Dehn, *J. Amer. Chem. Soc.*, 1924, **34**, 1402), or by acetylating compounds related to acetamide such as acetonitrile (Gautier, *Compt. rend.*, 1868, **67**, 1256), *N*-acetyl-*N'*-methylurea (Hofmann, *Ber.*, 1881, **14**, 2731), and potassium cyanate or thiocyanate (Brunner, *Ber.*, 1914, **47**, 2671). Strecker, Lindemann, and Franchimont have reported very low yields in their syntheses. Hentschel investigated some of the causes of such low yields and devised a method which permits the preparation of diacetimide in useful quantities. The methods of Titherley, Rakshit, Brunner, and Dehn give comparable yields but at considerably higher cost. The authors have found that when Hentschel's method of reaction between acetamide and acetic anhydride is adopted and hydrogen chloride is used as a catalyst excellent yields of diacetimide are obtained. Hydrogen chloride may be introduced as dry gas or as one of the hydrochlorides of acetamide. A small amount of acetyl chloride has a similar effect but the yield is lower and the diacetimide is less pure than in the former cases. It is interesting to compare this modified Hentschel synthesis with the acetylation of hydrogen sulphide by acetic anhydride to thioacetic acid, which does not take place unless small quantities of hydrogen chloride or acetyl chloride are present (Clarke and Hartmann, *J. Amer. Chem. Soc.*, 1924, **46**, 1731).

Hentschel suggested that acetamide is acetylated by acetic anhydride. In the reaction catalysed by hydrogen chloride this is surely not the only process that takes place. Transient formation of ammonium chloride in early stages of the catalysed reaction is in better agreement with a mechanism in which ammonia is eliminated from two molecules of acetamide. Titherley (*loc. cit.*, p. 411) found that much bisacetamide hydrochloride is formed when acetamide is treated with acetyl chloride in boiling benzene solution and the yield of diacetimide is low. On completing Dehn's experiment of treating acetamide with acetyl chloride in cold ether, we found that the reaction proceeds almost quantitatively according to the equation $3NH_2Ac + AcCl = NHAc_2 + 2NH_2Ac,HCl$. When Titherley's experimental conditions were modified

by using boiling xylene instead of benzene, the yield of diacetimide increased and less acetamide was recovered in the form of bisacetamide hydrochloride. In other words, acetylation is favoured at low temperatures and condensation at higher temperatures. Further supports for the condensation theory and the comparative difficulty of acetylation are furnished by the observations that bisacetamide hydrochloride is not decomposed by refluxing with ethyl acetate but yields diacetimide when refluxed with amyl acetate, and that azeotropic acetylation of acetamide does not yield diacetimide. On the other hand, high yields of diacetamide obtained by the modified Hentschel process indicate that elimination of ammonia from 2 mols. of acetamide cannot be the only reaction and not less than one third of the available acetamide molecules must react by the acetylating process. Recent experiments on the synthesis of mixed diacylimides (to be published shortly) show that in some cases the principal process is acylation, and in others, elimination of ammonia from two amide molecules. The latter reaction may be initiated by the formation of oxonium compounds, which will be discussed more fully later.

Since a single mechanism is unlikely, it is best to state yields in terms of diacetimide obtained from 100 parts of acetamide. In the following table the column headed NH_2Ac shows the recovery of acetamide either in free form or as bisacetamide hydrochloride. Experiments marked *A* are original experiments; those marked with *B* refer to claims of previous authors. Previously described experiments which have been checked or repeated with only minor alterations are marked *C*.

No.	Reagents.	$NHAc_2$, as % of original	NH_2Ac, as % of original NH_2Ac.	Notes.
1 *B*	NH_2Ac–Ac_2O	50	—	$Ac_2O : NH_2Ac = 1{\cdot}16 : 1$
2 *C*	do.	33	6	do.
3 *A*	$2HN_2Ac,HCl$–Ac_2O	90	2	$Ac_2O : NH_2Ac = 0{\cdot}98 : 1$
4 *A*	do.	129	0	$Ac_2O : NH_2Ac = 1{\cdot}29 : 1$
5 *A*	do.	95	10	HCl passed into Ac_2O
6 *A*	NH_2Ac,HCl–Ac_2O	124	3	$Ac_2O : NH_2Ac = 1{\cdot}33 : 1$
7 *A*	NH_2Ac–$2NH_2Ac,HCl$–Ac_2O	120	0	$HCl : NH_2Ac = 1 : 12$
8 *A*	NH_2Ac–AcOH–BuOAc	0	45	Azeotropic distilln.
9 *A*	$2NH_2Ac,HCl$–EtOAc	0	100	—
10 *A*	$2NH_2Ac,HCl$–AmOAc	18	4	—
11 *B*	NHNaAc–AcCl	78	—	—
12 *B*	NH_2Ac–AcCl	17—21	—	In boiling benzene
13 *C*	do.	42	9	In boiling xylene
14 *C*	do.	34	80	In ether
15 *C*	do.	14	74	In benzene
16 *B*	NH_2Ac–Na–alc. HCl	[Overall yields not clearly stated]		
17 *B*	KOCN–Ac_2O	60—80	—	Yield as % of KOCN
18 *B*	KSCN–Ac_2O	32	—	Yield as % of KSCN

1, 2; Hentschel, *loc. cit.* 11; Titherley, *J.*, 1901, **79**, 391. 12, 13; *Idem, ibid.*, p. 411. 14, 15; Dehn, *loc. cit.* 16; Rakshit, *loc. cit.* 17, 18; Brunner, *loc. cit.*

The advantage of laboratory methods based on experiment 7 is obvious. Comparatively large quantities of diacetimide have been prepared by this method.

Experimental.

In order to save space no details are given for experiments checking previously published methods or for the purification of well-known reagents. Numbers preceding experiments refer to the table.

(3) Bisacetamide hydrochloride (Found: HCl, 23·24. Calc.: HCl, 23·62%), m. p. 128—135° (35 g.), was refluxed with freshly distilled acetic anhydride (45·4 g.) for 30 mins. Fractions boiling up to 125° were removed and the residue was distilled in a vacuum. The fraction of b. p. 104—106°/6 mm. was dissolved in 150 c.c. of ether. Dry hydrogen chloride precipitated some bisacetamide hydrochloride from this solution. The precipitate was filtered off, and the filtrate was freed from hydrogen chloride by treatment with barium carbonate (5 g.) and anhydrous potassium carbonate (5 g.) in succession. On removal of the ether, diacetimide (25 g.) was obtained; m. p. 78° (Found: N, 13·9. Calc.: N, 13·95%). Diacetimide (5 g.) was converted into sodium diacetimide by 30 mins.' refluxing with sodium (3 g.) in anhydrous ether (150 c.c.), 16 hours' standing, and another 30 mins.' refluxing. After filtration the ether was evaporated at 34°. No residue was obtained; hence the product was free from triacetamide.

(4) Bisacetamide hydrochloride (8·2 g.) and acetic anhydride (14·0 g.), treated as above, afforded 8·1 g. of diacetimide, m. p. 78°, free from triacetyl compound.

(5) Acetamide (30 g.) was suspended in acetic anhydride (64·5 g.). Dry hydrogen chloride was passed into the suspension until the weight increased by 9·3 g. The mixture was worked up as in the previous experiments, affording 28·5 g. of diacetimide, m. p. 78°, free from triacetyl compound.

(6) Acetamide (70 g.) was dissolved in about 350 c.c. of chloroform. The solution was treated with dry hydrogen chloride for 2½ hours. The precipitated crystals were filtered off and dried by suction; yield, 113 g. (Found: HCl, 34·9. Calc. for NH_2Ac,HCl: Cl, 38·2%). When a small sample (0·7 g.) was kept in 150 c.c. of chloroform for 3 hours, the HCl content was reduced to 33·0%. Freshly prepared

acetamide hydrochloride (10·0 g.) and acetic anhydide (14·0 g.) were treated as in previous experiments, yielding 8·1 g. of diacetimide, m. p. 78°, and 0·2 g. of bisacetamide hydrochloride.

(7) Acetamide (30·0 g.), bisacetamide hydrochloride (7·5 g.), and acetic anhydride (75·6 g.) were treated as in previous experiments, affording 42·8 g. of diacetimide; no bisacetamide hydrochloride was formed. Acetamide (200 g.), acetic anhydride (408 g.), and bisacetamide hydrochloride (20 g.) were worked up as in previous experiments but the crude product was collected at 105—112°/10 mm. Hardly any bisacetamide hydrochloride was formed. The residue from the ether was redistilled at 104—106°/7 mm., some material being discarded during the final distillation to safeguard purity (m. p. 79°; content of triacetyl component less than 0·005%). Crude yields varied between 240 and 280 g., and those of pure diacetimide between 200 and 240 g. When acetyl chloride (20 g.) was used instead of bisacetamide hydrochloride, 180 g. of diacetimide, m. p. 76—77°, were obtained. Much acetonitrile and high-boiling residue were formed.

(8) Acetic acid (204 g.) and *n*-butyl acetate (183 g.) were slowly distilled through a 4 ft. fractionating column. After 50 c.c. had been distilled off without evidence of water coming over, acetamide (100 g.) was added to the mixture and distillation was continued for six hours at a constant b. p. of 124°. The residue was worked up by the usual procedure. No diacetimide was obtained.

(9) Bisacetamide hydrochloride (30·0 g.) and ethyl acetate (62 c.c.) were refluxed for 20 hours. No change occurred.

(10) Bisacetamide hydrochloride (20·0 g.) and technical *iso*amyl acetate (b. p. 120—140°) (100 g.) were refluxed for 2 hours. Ammonium chloride (5·6 g.) was filtered off. The residue was worked up in the usual manner and yielded acetamide (0·5 g.), bisacetamide hydrochloride (0·3 g.), and diacetimide (2·8 g.).

(13) Acetamide (18 g.), acetyl chloride (26 g.), and xylene (100 c.c.) were heated under reflux for 60 mins. Fractionation yielded ammonium chloride (3·0 g.), bisacetamide hydrochloride (2·2 g.), and diacetimide (7·5 g.; m. p. 72—74°). 0·1 G. of an unidentified low-melting substance, not acetamide or diacetimide, was obtained from a fraction of b. p. 60—100°/8 mm.

(14, 15) Acetamide (18 g.) and acetyl chloride (8 g.) were mixed in ether (200 g.) or benzene (100 c.c.), kept for 2½ hours, heated for 10 mins. near the b. p. of the solvent, and then set aside for 3 days. Crystals of bisacetamide hydrochloride were obtained by filtering and washing with warm chloroform. The chloroform removed unreacted acetamide. More unreacted acetamide was precipitated by dry hydrogen chloride from the original solutions. Removal of the solvents gave diacetimide of poor quality, m. p. 40—50°. Total yields: bisacetamide hydrochloride, 15·3 g. from ether and 15·5 g. from benzene; unreacted and undissolved acetamide, 2·0 g. from ether, 1·4 g. from benzene; dissolved acetamide precipitated as bisacetamide hydrochloride, 0·5 g. from ether, 0·1 g. from benzene; impure diacetimide, 6·1 g. from ether, 2·5 g. from benzene. The reaction in benzene yielded acetonitrile, which was not isolated.

UNIVERSITY OF TASMANIA, HOBART

[*Received, July 7th*, 1947.]