Studies in Reductive Amination. Part II.[1] Aminopivalic Acid from Hydroxypivalic Acid

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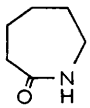
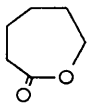
Low yields (*ca.* 20%) of aminopivalic acid result when hydroxypivalic acid is catalytically hydrogenated in aqueous ammonia at 225° and 220 atmospheres pressure. Dealdolisation products also are produced in substantial quanitities, and in the absence of catalyst and hydrogen these are formed exclusively.

RECENTLY, processes for the production of the important polyamide intermediate 6-hexanolactam (I), which involve amination of 6-hydroxyhexanoic acid (II), 6-hexanolactone (III), and their polymeric derivatives, have been disclosed in numerous patents. Thus the hydroxy-acid or derivatives may be heated at high temperature and under high pressure (*a*) with an excess of aqueous ammonia in the absence [2] or presence of a catalyst, *e.g.*, ammonium chloride,[3] or (*b*) with excess anhydrous [4] or aqueous ammonia [5] in the presence of hydrogen and a hydrogenation catalyst. Usually the product (I) is isolated by extraction with solvent (*e.g.*, chloroform) and aqueous residues are returned to the pressure vessel for further processing. We now report attempts to convert hydroxypivalic acid (IV; R = OH) by analogous techniques to aminopivalic acid (V) and/or pivalolactam (VI), which are intermediates for the synthesis of fibre-forming polyamides.[6]

Hydroxypivalic acid (IV; R = OH) has been heated under autogenous pressure with aqueous ammonia (5—10 mol.) at temperatures of from 200 to 390°. At 200° hydroxypivalamide (IV; R = NH_2) was the sole product, but at 240° and higher temperatures, under pressures of up to 320 atmospheres, extensive decomposition occurred and a variety of products was isolated including isobutyric acid (VII; R = OH), isobutyramide



(I)

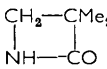


(III)

$HO{\cdot}[CH_2]_5{\cdot}CO_2H$ (II)

$HO{\cdot}CH_2{\cdot}CMe_2{\cdot}COR$ (IV)

$H_2N{\cdot}CH_2{\cdot}CMe_2{\cdot}CO_2H$ (V)



(VI)

$Me_2CH{\cdot}COR$ (VII)

(VII; R = NH_2), methylamine, isobutylamine, the *N*-alkyl isobutyramides (VII; R = NHMe) and (VII; R = $NH{\cdot}CH_2{\cdot}CHMe_2$), and olefinic material (propene ?). Aminopivalic acid (V) and pivalolactam (VI) were not formed under these conditions. However, when hydroxypivalic acid (IV; R = OH) was treated at 175—225° with excess of 14% aqueous ammonia (6·25 mol.) in the presence of hydrogen under 160—225 atmospheres

[1] Part I, D. H. Johnson, *J. Chem. Soc.* (*C*), 1967, 1284. Some of the findings of the present investigation are the subject of Patent Application No. 11,954/1967.

[2] U.S.P. 2,840,553—4/1958; 3,000,877/1961; 3,000,879—80/1961; F.P. 1,417,171/1965.

[3] F. P. 1,389,608/1965; 1,419,684/1965.

[4] U.S.P. 2,817,646/1957; F.P. 1,425,954/1966.

[5] F.P. 1,388,284/1965; 1,396,249/1965.

[6] B.P. 601,123/1948.

pressure and a hydrogenation catalyst, *e.g.*, Raney nickel, platinic oxide, or copper–barium chromite, the amino-acid (V) was produced in an optimum yield of approximately 20% at about 50—70% conversion of the hydroxy-acid (IV; R = OH). Isobutyramide (VII; R = NH_2) was the principal product under hydrogenation conditions, the yield falling from *ca.* 70% at 175° to *ca.* 15% at 275°; at the latter temperature, methylamine and isobutyric acid were the only additional products, there being no traces of aminopivalic acid (V) or the *N*-alkyl isobutyramides (VII; R = NH·Me) or (VII; R = NH·CH_2·$CHMe_2$). Isobutyramide and methylamine also were the main products when hydroxypivalic acid was treated at 225° with anhydrous ammonia and hydrogen in the presence of Raney nickel.

Clearly, methylamine and isobutyric acid and its amide derivatives are, or are derived from, fragments of dealdolisation of the HO·CH_2·CMe_2 segment of hydroxypivalic acid, whilst isobutylamine must arise from a sequence involving decarboxylation of the ·CH_2·CMe_2·CO_2H portion of the molecule. The *N*-alkyl amides (VII; R = NHMe) and (VII; R = NH·CH_2·$CHMe_2$) are artefacts resulting from reaction of isobutyric acid with by-product methylamine and isobutylamine.

The inherent instability of the HO·CH_2·CMe_2 group has been observed previously [7] (i) during reductive amination of hydroxypivalaldehyde (VIII) which yielded methylamine, isobutylamine, and water, and (ii) when

HO·CH_2·CMe_2·CHO (VIII) H–[O·CH_2·CMe_2·CO]$_m$–OBu^n (IX)

butyl poly(hydroxypivalate) (IX) was degraded completely to formaldehyde, propene, and carbon monoxide by prolonged heating at 200—220° with sodium titanium butoxide.

EXPERIMENTAL

Paper chromatograms were run by the descending technique on unwashed Whatman No. 1 paper. For bases and amino-acids the solvent system was the upper layer of an equilibrated mixture of butan-1-ol–acetic acid–water (4 : 1 : 5 v/v) and ninhydrin was the spray reagent. For aliphatic acids, butan-1-ol saturated with 1·5N-ammonia solution was solvent and ethanolic bromocresol green the spray reagent.

Hydroxypivalic Acid (IV; R = OH).—Prepared from the cyclic dimer of hydroxypivalaldehyde [8] by the Cannizzaro reaction,[9] or by oxidation with 30% hydrogen peroxide,[10] this acid separated from benzene–light petroleum (60—80°) as colourless needles, m. p. 125—125·5° (Found: C, 50·8; H, 8·3%; Equiv., 118·5. Calc. for $C_5H_{10}O_3$: C, 50·8; H, 8·5%; Equiv., 118·1).

Aminopivalic Acid (V).—Prepared by hydrolysis of ethyl 3-formylamino-2,2-dimethylpropionate with aqueous barium hydroxide,[11] this amino-acid (V) had m. p. 239° (Found: C, 51·2; H, 9·5; N, 11·8. Calc. for $C_5H_{11}NO_2$: C, 51·3; H, 9·5; N, 12·0%) (lit.,[11] m. p. 239—241°). The *toluene*-p-*sulphonyl derivative* of (V) (1·9 g.), prepared from the amino-acid (1·0 g.) and toluene-*p*-sulphonyl chloride (2·0 g.) by the method of McChesney and Swann,[12] formed small colourless needles, m. p. 147—148° from 60% aqueous ethanol (Found: C, 52·7; H, 6·4; N, 5·1; S, 11·1. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·3; N, 5·2; S, 11·8%).

Amination of Hydroxypivalic Acid with Aqueous Ammonia.—(a) *Procedure.* Recrystallised hydroxypivalic acid (78 g., 0·66 mole) and 14% aqueous ammonia (400—800 ml., 3·30—6·60 moles) were charged to a Bergius autoclave (capacity 1500 or 2000 ml.), which was purged with nitrogen and then heated at the required temperature within the range 200—390° for 3—4 hr. After cooling, the contents of the autoclave, which had a strong olefinic odour, were discharged with the aid of water and then extracted continously with ether for 2—3 days. The ether extracts and extracted aqueous liquors then were examined by the procedures described in (b). Data relating to reaction conditions and yields of products obtained in the several experiments undertaken are summarised in Table 1. Apart from the reaction at 200° (experiment 1) in which hydroxypivalamide was the main product, extensive decomposition occurred to approximately the same pattern in all the other reactions, and overall recoveries of products were generally in the range 55—63%, owing to loss of volatile products, *e.g.*, amines, CO_2, etc., during opening of the autoclave or acidification stages of the work-up procedure.

(b) *Isolation of products.* (i) *Isobutyramide* (from experiments 2—6 inclusive, Table 1). The oily residues (30—40 g.), which remained when the dried ethereal extracts from these reactions were evaporated, partly crystallised on keeping. The crystalline components (5—10 g.) were filtered off, washed with light petroleum (60—80°), and recrystallised from benzene to yield isobutyramide as colourless plates, m. p. and mixed m. p. 127—128° (Found: C, 55·5; H, 10·4; N, 15·7. Calc. for C_4H_9NO: C, 55·1; H, 10·4; N, 16·1%) (i.r. and mass spectra).

(ii) N-*Alkylisobutyramides* (from experiments 2—6 inclusive, Table 1). The oily filtrates remaining after removal of isobutyramide were combined with the oily residues obtained by evaporation of the benzene mother-liquors from the recrystallisation of this amide, and the products then distilled *in vacuo*. In each case the main bulk of distillate (5—9 g.) had b. p. 60—65°/0·05 mm., n_D^{25} 1·4361 (Found: C, 63·2; H, 11·2; N, 12·6. Calc. for $C_5H_{11}NO$: C, 59·4; H, 11·0; N, 13·85. Calc. for $C_8H_{17}NO$: C, 67·1; H, 12·0; N, 9·8%), $\nu_{max.}$ 3333, 1639, and 1550 cm.$^{-1}$ (–CO·NH–). The mass spectrum indicated the presence of two compounds, a major component of molecular formula $C_5H_{11}NO$ (*m/e* 101) and a minor component $C_8H_{17}NO$ (*m/e* 143).

These mixed amides (1·0 g.) were boiled under reflux for 2 hr. with concentrated hydrochloric acid (20 ml.), the resulting solutions then were diluted with water and extracted continuously with ether for 24 hr. When evaporated, the dried ether extracts yielded isobutyric acid (*ca.* 0·6 g.) (paper chromatography). The residual aqueous hydrolysates, which contained the hydrochlorides of 2

[7] H. J. Hagemeyer and G. C. DeCroes, ' The Chemistry of Isobutyraldehyde,' Tennessee Eastman Co., Kingsport, Tennessee, 1953, p. 18.

[8] E. T. Stiller, S. A. Harris, J. Finkelstein, J. C. Keresztesy, and K. Folkers, *J. Amer. Chem. Soc.*, 1940, **62**, 1787; E. Spath and I. v. Szilagyi, *Ber.*, 1943, **76***B*, 949.

[9] E. R. Alexander, *J. Amer. Chem. Soc.*, 1948, **70**, 2592.

[10] H. P. Franck and K. Krzemicki, *Monatsh.*, 1964, **95**, 410.

[11] B.P. 601,142/1948.

[12] E. W. McChesney and W. K. Swann, *J. Amer. Chem. Soc.*, 1937, **59**, 1116.

bases, methylamine (major component) and isobutylamine (minor component) (paper chromatography), were basified with 2N-sodium hydroxide solution and boiled under reflux whilst a slow stream of nitrogen was led through. Off-gases were passed into solutions of picric acid in ether containing a little methanol and the yellow precipitates (0·3—0·4 g.) which formed were filtered off and recrystallised from methanol to yield methylamine picrate, m. p. and mixed m. p. 209° (Found: C, 32·2; H, 3·4; N, 21·1. Calc. for $C_7H_8N_4O_7$: C, 32·3; H, 3·1; N, 21·5%).

Direct comparison of the i.r. and mass spectra of the mixed amides with corresponding spectra of authentic *N*-methylisobutyramide (VII; R = NHMe) and *N*-isobutylisobutyramide (VII; R = NH·CH_2·$CHMe_2$) indicated the mixture to have a 65 : 35 w/w composition.

(iii) *Hydroxypivalamide* (IV; R = NH_2) (from experiment 1, Table 1). When the dried ethereal solution obtained by continuous extraction of the total crude product from the reaction performed at 200° (experiment 1, Table 1) was evaporated, there remained an oily mass (15·1 g.) which crystallised during storage and then had m. p. 72—80°. Purified from benzene, this material separated in small colourless *needles*, m. p. 87—89° (Found: C, 52·1; H, 9·5; N, 11·8. $C_5H_{11}NO$ requires C, 51·3; H, 9·5; N, 12·0%), $\nu_{max.}$ 3413, 1653 (–CO·NH_2), 1036 (–CH_2·OH), and doublet near 1370 $cm.^{-1}$ (–CMe_2). The mass spectrum contained no parent ion, but fragmentation ions at *m/e* 31 (–CH_2·OH), 44 (–CO·NH_2), and 41 (C_3H_5) supported formula (IV; R = NH_2).

Hydroxypivalamide was not detected amongst the products of amination reactions conducted at temperatures above 200°.

(iv) *Isobutyric acid* (from experiments 3—6, Table 1). The ether-extracted aqueous amination liquors (amide-free) were acidified with hydrochloric acid and extracted continuously with ether for 48 hr. The dried ether extracts were evaporated and the residue, when distilled, yielded isobutyric acid (5—10 g.), b. p. 149—154°, n_D^{25} 1·3918; the *p*-toluidine derivative had m. p. and mixed m. p. 108—109°.

Ether extraction of analogous acidified amination liquors from experiments 1 and 2 (Table 1), which were conducted at 200 and 240°, yielded unchanged hydroxypivalic acid, m. p. and mixed m. p. 125°, and no isobutyric acid.

(v) *Primary amines and aminopivalic acid* (from experiments 2—6, Table 1). The acidic aqueous residues which remained after removal of isobutyric acid or unreacted hydroxypivalic acid [as in (iv)] were evaporated to dryness on a steam-bath and yielded green hygroscopic crystals (4—20 g.). Paper chromatographic examination of these mixed hydrochlorides showed methylamine to be the principal base present; isobutylamine was present in much smaller amounts along with trace quantities of aminopivalic acid and an unidentified base.

Reductive Amination of Hydroxypivalic Acid with Aqueous Ammonia and Hydrogen in the Presence of Hydrogenation

TABLE 1

Amination of hydroxypivalic acid (78 g., 0·66 mole) with 14% aqueous ammonia at 200—395°

		Conditions			Hydroxypivalic acid unchanged		
Expt.	14% aq. ammonia used g. (moles)	Max. temp.	Max. pressure (atmos.)	Time at max. temp. (hr.)	g.	mole	%
1	400 (3·30)	195—200°	20	3	52·6	0·446	67·7
2	800 (6·60)	238—240	51	3·5	25·0	0·212	32·1
3	400 (3·30)	267—272	87	3	—	—	—
4	800 (6·60)	323—325	152	3	—	—	—
5	800 (6·60)	367—368	320	4	—	—	—
6	400 (3·30)	386—390	245	3	—	—	—

	Yields of products (on hydroxypivalic acid reacted)											
	Primary amide *			Isobutyric acid			Mixed secondary amides			Hydrochlorides of bases †			Total isolated materials
	g.	mole	%	g.	mole	%	g.	mole	%	g.	mole	%	%
1	15·1	0·129	60·3	—	—	—	—	—	—	—	—	—	60·3
2	5·3	0·061	13·6	—	—	—	5·9	0·058	13·0	20·9	0·301	69·1	95·7
3	8·5	0·098	14·8	6·1	0·069	10·5	16·0	0·016	24·0	6·0	0·089	13·5	62·8
4	8·8	0·101	15·3	9·6	0·109	16·5	10·1	0·100	15·2	4·0	0·059	9·0	56·0
5	9·7	0·112	16·9	7·3	0·084	12·6	10·2	0·101	15·3	4·6	0·068	10·3	55·1
6	8·5	0·098	14·8	4·5	0·051	7·8	15·1	0·150	22·7	3·8	0·056	8·5	53·7

* Expt. 1, hydroxypivalamide; expts. 2—6, isobutyramide. † Calc. as $MeNH_2$,HCl.

Catalysts.—(a) *General procedure.* Hydroxypivalic acid (78 g., 0·66 mole) in 14% aqueous ammonia (500 ml., 4·12 moles) was stirred at room temperature for 2 days with W2 Raney nickel catalyst (10 g.).[13] Catalyst was filtered off and the filtrate was charged to a 2000 ml. capacity Bergius autoclave along with fresh catalyst (10 g.), *e.g.*, more W2 Raney nickel, or platinic oxide, or copper–barium chromite, as required. Hydrogen was admitted to the autoclave until the total pressure was about 100 atmospheres. The bomb then was heated at the required temperature (in the range 175—275°) for 8 hr., cooled, and the product discharged with the aid of water. Data relating to the experimental conditions used in the various reactions are collected in Table 2.

After catalyst had been filtered off, the brown filtrates were extracted continuously with ether for 2 days and the dried ethereal extracts, when evaporated, yielded brown crystalline masses (3—15 g.) which were purified from benzene and afforded isobutyramide, m. p. and mixed m. p. 127°.

(b) *Isolation of aminopivalic acid. Method A.* The total aqueous liquors (from experiments 1—3 and 5—7, Table 2) were evaporated *in vacuo* until excess of ammonia and water had been removed. Aqueous solutions of the

[13] R. Mozingo, *Org. Synth.*, Coll. Vol. III, p. 181.

oily residues (30—70 g.) were acidified with concentrated hydrochloric acid and extracted continuously for 2 days with ether. The residues which remained after evaporation of the solvent from the dried extract, were freed from small amounts of fatty acid contaminants at 60°/10 mm. and then recrystallised from benzene to give unchanged hydroxypivalic acid (11—65 g.), m. p. and mixed m. p. 123—125°.

When this procedure was applied to the product from experiment 5, Table 2, isobutyric acid (7·1 g.), b. p. 153—154°, n_D^{22} 1·3911, was isolated instead of hydroxypivalic acid.

The aqueous liquors, which remained after organic acids had been extracted, were concentrated to small bulk, ammonium chloride was removed by fractional crystallisation, and when the final filtrates were evaporated to dryness at 70° *in vacuo* green-brown crystalline masses (4—23 g.), consisting of the mixed hydrochlorides of methylamine, isobutylamine, and aminopivalic acid (paper chromatography), remained. The aminopivalic acid content of the mixtures was assessed semi-quantitatively by direct comparison of the paper chromatographic spots with the intensities of spots produced by known quantities of the pure amino-acid (VI), applied as 1% aqueous solutions.

The mixed base hydrochlorides from experiment 2, Table 2 (6·8 g. from a total of 27·8 g.) were separated by ion-exchange on Amberlite IRA-400 resin (OH^- form; 600 ml.). Isobutylamine and methylamine were eluted from the column with water (2000 ml.), whilst aminopivalic acid was removed with 4% aqueous sodium hydroxide. The alkaline eluates (1200 ml.) were concentrated to small bulk by heating on a steam-bath, then acidified with concentrated hydrochloric acid, and again evaporated to small bulk. Sodium chloride crystals which separated during cooling were removed and the filtrate was reduced to a volume of 20 ml. A solution of this concentrated filtrate (5 ml.) in water (15 ml.) was basified with 2N-sodium hydroxide (20 ml.) and stirred at room temperature for 3½ hr. with toluene-*p*-sulphonyl chloride (4·0 g.) in ether (50 ml.). The ether layer was removed, the aqueous liquors were acidified, and the colourless precipitate was filtered off and dried. The toluene-*p*-sulphonyl derivative of aminopivalic acid formed small colourless needles (1·4 g.) from 60% aqueous ethanol, m. p. and mixed m. p. 144—147° (Found: C, 52·7; H, 6·4; N, 5·3; S, 11·3%) (i.r. spectrum).

Method B (experiment 4, Table 2). The aqueous liquors which remained after removal of isobutyramide (9·8 g.) by ether-extraction of the products from experiment 4, Table 2 were evaporated under reduced pressure to remove water and excess of ammonia. The residual light brown oil (64·9 g.) was redissolved in water and acidified with 5N-sulphuric acid and the solution was extracted continuously with ether for 24 hr. When solvent was evaporated, the dried ethereal extract yielded a crystalline mass of hydroxypivalic acid (41·9 g.), m. p. and mixed m. p. 123° (from benzene). The extracted aqueous liquors were diluted with water to 300 ml., then warmed to 40—50° and treated with an aqueous slurry of $Ba(OH)_2,8H_2O$ (90 g. in 100 ml. H_2O). 2N-Sulphuric acid (50 ml.) was added, precipitated barium sulphate (52·6 g.) was removed, and the filtrate was saturated with carbon dioxide. The precipitate of barium carbonate (11·7 g.) was filtered off, and the aqueous liquors, on evaporation at 15 mm., yielded a colourless crystalline residue (11·4 g.) which was extracted with boiling ethanol. The cooled extract deposited small crystals (6·9 g.) which were purified further by solution in ethanol (50 ml.) and water (15 ml.) and subsequent reprecipitation with ether (150 ml.). Aminopivalic acid was thus obtained as small, colourless needles (5·6 g.), m. p. and mixed m. p. 239—240° (Found: C, 52·1; H, 9·5; N, 11·8%) (i.r. spectrum).

TABLE 2

Reductive amination of hydroxypivalic acid (78 g., 0·66 mole) with 14% aqueous ammonia (500 ml.) at 175—275°

Expt.	Catalyst	g.	Max. temp. (°)	Max. pressure (atmos.)	Hydrogen absorbed (mole)	Hydrogen absorbed g.	Hydroxypivalic acid unchanged mole	Hydroxypivalic acid unchanged %
1	W2 Raney nickel	10	175	162	0·408	64·8	0·549	83·2
2	W2 Raney nickel	10	220		1·046	30·4	0·258	39·0
3	W2 Raney nickel	10	225	224	0·758	33·1	0·281	42·5
4	W2 Raney nickel	10	225	205	0·174	41·9	0·355	53·8
5	W2 Raney nickel	10	275	268	1·802	—	—	—
6	PtO_2	4·7	225	216	2·012	11·2	0·095	14·4
7	Copper–barium chromite	10	225	218	0·292	21·8	0·185	28·0

	Yields of products (on hydroxypivalic acid reacted)								
	Isobutyramide			Isobutyric acid			Aminopivalic acid		
Expt.	g.	mole	%	g.	mole	%	g.	mole	%
1	6·8	0·078	70·6	—	—	—	0·75 *	0·006	5·8
2	11·5	0·132	32·6	—	—	—	5·3 ‡	0·045	11·3
3	5·8	0·067	17·6	—	—	—	7·0 *	0·060	15·8
4	9·8	0·113	36·9	—	—	—	6·9 †	0·059	19·4
5	8·7	0·100	15·2	7·1	0·081	12·2	— §	—	—
6	4·5	0·052	9·15	—	—	—	5·0 *	0·043	7·6
7	5·5	0·063	13·3	—	—	—	9·0 *	0·076	16·3

* Estimated chromatographically. † Isolated by ion-exchange chromatography. ‡ Estimated from isolated yield of toluene-*p*-sulphonyl derivative. § Methylamine was isolated in 6% yield.

Reductive Amination of Hydroxypivalic acid with Anhydrous Ammonia and Hydrogen in the Presence of Raney Nickel at 225°.—Hydroxypivalic acid (63·3 g., 0·536 mole) in excess 14% aqueous ammonia was evaporated to dryness *in vacuo*. The dry crystalline residue was charged to a Bergius autoclave (1500 ml. capacity) together with anhydrous ammonia (140 g., 8·24 moles) and W2 Raney nickel catalyst (10 g.) and hydrogen gas was admitted until the total initial pressure was 100 atmos. The bomb was then heated at 225° for 8 hr. (max. pressure developed 285 atmos.) when

hydrogen (0·612 mole) was absorbed. After cooling, the product was washed out of the autoclave with methanol, catalyst was filtered off, and the filtrate was evaporated. The residual mass of brown crystals (32·0 g.), when purified from benzene, yielded isobutryamide, colourless plates, m. p. and mixed m. p. 127° (i.r. spectrum). When the methanol distillate was acidified with concentrated hydrochloric acid and then evaporated to dryness there remained a crystalline residue (28·4 g.). These mixed hydrochlorides contained the salts of methylamine (major component) and isobutylamine (minor component) (paper chromatography). No aminopivalic acid was produced.

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