[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE WESTVACO CHLOR-ALKALI DIVISION AND THE CENTRAL RESEARCH LABORATORY OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

α-Oximino Ketones. III. A New Synthesis of α-Amino Acids[1]

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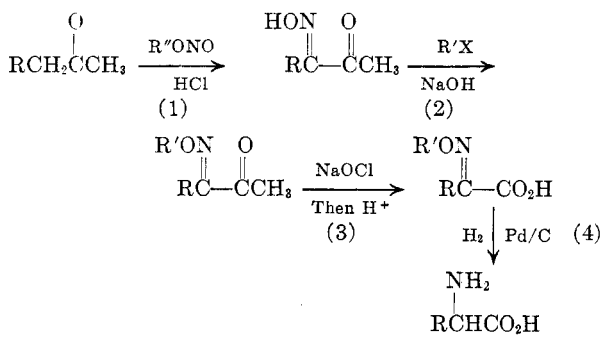
The reaction of α-alkoximino methyl ketones with aqueous sodium hypochlorite has been found to give α-alkoximino acids in good yield. This reaction is the key step in a new synthesis of α-amino acids from methyl ketones, which involves nitrosation of the ketone, alkylation of the resulting α-oximino ketone, cleavage of the resulting α-alkoximino ketone with hypochlorite, and reduction of the resulting α-alkoximino acid to an α-amino acid. Overall yields of α-amino acids from methyl ketones ranged from 14 to 63%.

In the course of a study of the reactions of α-alkoximino ketones it was found that α-alkoximino methyl ketones readily undergo the haloform reaction with aqueous sodium hypochlorite to give chloroform and the corresponding α-alkoximino carboxylic acids in good yield. This discovery has been developed into a new and quite general synthesis of α-amino acids from methyl ketones, comprising the steps of (1) nitrosation of the methyl ketone, (2) alkylation of the resulting α-oximino ketone, (3) cleavage of the resulting α-alkoximino ketone with alkaline hypohalite, and (4) reduction of the resulting α-alkoximino acid to an α-amino acid. The synthesis is presented in generalized equation form below:

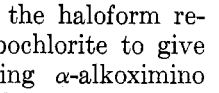


Overall yields of α-amino acids from methyl ketones were: norleucine, 63% from 2-heptanone; phenylalanine, 50% from 1-phenyl-3-butanone; valine, 34% from 4-methyl-2-pentanone; and alanine, 14% from 2-butanone. The last yield is not regarded as representative because the volatility of the intermediates made mechanical losses high.

The nitrosation reaction (step 1) is a well known one and can be carried out in several ways, amply documented in a recent review.[2] Treating a solution of the methyl ketone in ether with methyl nitrite in the presence of a small amount of hydrochloric acid was found to be a satisfactory technique for the ketones used in this study. The α-oximino ketones prepared are described in Table I.

TABLE I

α-OXIMINO KETONES



R	Yield, %	Melting Point, °C.[a] Found	Lit.
—$(CH_2)_3CH_3$	78	59–60	...[b]
—$CH(CH_3)_2$	68	78–79	75[c]
—CH_3	48	75.5–76.5	76.5[d]
—$CH_2C_6H_5$	75	80–81	80–81[e]
—C_6H_5	91	162–163	164–165[f]

[a] All melting points are uncorrected. [b] *Anal.* Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.25; N, 9.77. [c] B. Westenberger, *Ber.*, **16**, 2991 (1883). [d] W. L. Semon and V. R. Damerell, *Org. Syntheses*, **Coll. Vol. II**, 204 (1943). [e] G. Ponzio, *Gazz. chim. ital.*, **35**, 394 (1905). [f] H. Rheinboldt and O. Schmitz-Dumont, *Ann.*, **444**, 130 (1925).

Although the alkylation of α-oximino ketones (step 2) has been described,[3] it was necessary to work out methods for carrying out the reaction in good yield. Since the nature of the alkyl group is unimportant because it is removed later in reduction, the method developed by Waters and Hartung[4] for the ethylation of α-oximino acids is very convenient. In applying this technique, the α-oximino ketone was dissolved in aqueous base and treated simultaneously with ethyl sulfate and equivalent base, usually at elevated temperature. A particular virtue of this method was that it permitted synthesis of α-ethoximino ketones from ketones without the necessity of isolating the intermediate α-oximino ketones. Thus, the ether solutions from the nitrosation reaction could be extracted with aqueous base, and the resulting solutions treated with ethyl sulfate as described to give the α-ethoximino ketones in yields of 50–75% from the corresponding ketones. Another procedure, capable of giving α-alkoximino ketones with a wide variety of alkyl groups, involved treating the sodium salt of the α-oximino ketone in aqueous methanol with an alkyl

(1) Paper I of this series: *J. Org. Chem.*, **24**, 580 (1959); Paper II: *Chem. & Ind. (London)*, 996 (1959).

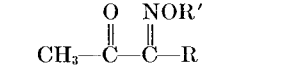
(2) O. Touster, *Org. Reactions*, **VII**, 327 (1953).

(3) M. Ceresole, *Ber.*, **16**, 833 (1883). O. Diels and G. Plaut, *Ber.*, **38**, 1917 (1905).

(4) K. L. Waters and W. H. Hartung, *J. Org. Chem.*, **12**, 469 (1947).

TABLE II

α-ALKOXIMINO KETONES

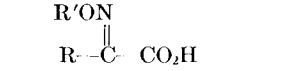


R	R′	Prep.[a] Method	Yield	B.P.[b] °C.	B.P.[b] Mm.	n_D^{35}	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
—$(CH_2)_3CH_3$	—CH_2CH_3	A	91	48.5–50	1.35	1.4325	63.12	10.01	8.18	63.38	9.86	8.46
		B	77									
		C	83									
—$(CH_2)_3CH_3$	—$CH_2C_6H_5$	D	81	104–106	0.6	1.5000	72.07	8.21	6.00	72.10	8.09	5.75
—$(CH_2)_3CH_3$	—CH_2CH_2—	C	58	133–135	0.55	1.4630	61.51	9.03	8.97	61.40	9.14	9.03
—$(CH_2)_3CH_3$	—CH_2CH_2OH	C	68	81–82	0.45	1.4590	57.73	9.15	7.48	57.85	8.93	7.30
—$CH(CH_3)_2$	—CH_2CH_3	B	51	60–61.5	15	1.4263	61.12	9.62	8.91	61.30	9.48	8.91
—$CH(CH_3)_2$	—$CH_2C_6H_5$	D	25	84–87	0.5	1.5017	71.20	7.82	6.39	71.56	7.80	6.37
—CH_3	—CH_2CH_3	C	68	42–42.5	13	1.4280	55.92	8.61	10.87	55.45	8.36	10.63
—CH_3	—$CH_2C_6H_5$	D	75	78–81	0.45[c]	1.5160	69.09	6.85	7.33	69.00	7.40	6.96
—$CH_2C_6H_5$	—CH_2CH_3	B	77	73–75	0.18	1.5069	70.22	7.37	6.83	70.42	7.48	6.95

[a] A = α-Oximino ketone + ethyl sulfate; B = nitrosation + alkylation with ethyl sulfate, overall yield; C = α-oximino ketone + alkyl bromide; D = α-oximino ketone + alkyl chloride. [b] All boiling points are uncorrected. [c] O. Diels and F. terMeer, *Ber.*, **42**, 1940 (1909) report b.p. 130° (12 mm.).

TABLE III

α-ALKOXIMINO ACIDS



R	R′	Yield	M.P., °C.[a]	B.P.[a] °C.	B.P.[a] Mm.	n_D^{35}	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. Neut. Equiv.	Found C	Found H	Found N	Found Neut. Equiv.
—$(CH_2)_3CH_3$	—CH_2CH_3	96	...	65–67	0.4[b]	1.4510	55.47	8.73	8.09	173.2	55.31	8.60	8.04	173.4
—$(CH_2)_3CH_3$	—CH_2CH_2—	74[c]	105.5–107[d]	...	...	...	53.15	7.65	8.86	158.2	53.22	7.78	8.89	159.3
—$CH(CH_3)_2$	—CH_2CH_3	74	...	53–53.5	0.5	1.4432	52.80	8.23	8.80	159.2	52.84	8.12	8.97	161.1
—CH_3	—CH_2CH_3	46	68–70[e]	73–76	2.1	...	45.79	6.92	10.68	131.1	45.95	6.71	10.71	132.8
—CH_3	—$CH_2C_6H_5$	36	84–85[f]	...	...	...	62.16	5.74	7.25	193.2	62.35	5.66	7.09	194.8
—CHC_6H_5	—CH_2CH_3	70	61–62[g]	...	...	...	63.75	6.32	6.76	207.2	64.00	6.18	6.88	206.8

[a] All melting points and boiling points are uncorrected. [b] Waters and Hartung[4] report b.p. 83–88° (1–3 mm.). [c] Conversion 19%. [d] Recrystallized from a mixture of water and ethanol. [e] Recrystallized from carbon tetrachloride. [f] Recrystallized from petroleum solvent (b.p. 65–67°). [g] Recrystallized from a mixture of carbon tetrachloride and petroleum solvent. Waters and Hartung[4] report m.p. 58.5–59°.

halide. The α-alkoximino ketones prepared are described in Table II.

The haloform reaction (step 3) was carried out using either a commercial 5.25% sodium hypochlorite solution or a solution of about 10% concentration made by adding chlorine to aqueous sodium hydroxide. The use of a cosolvent such as dioxane to improve the miscibility of the organic and aqueous phases was helpful in giving better yields. Experiments with reaction conditions indicated that best results were obtained by adding the cosolvent and the α-alkoximino ketone to the aqueous hypochlorite at room temperature or below, and allowing the mixture to warm spontaneously while stirring vigorously to insure good mixing. Cooling was applied if the temperature of the mixture exceeded 75°. The acids prepared are described in Table III.

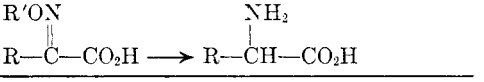
In addition to the α-alkoximino acids listed in Table III, α-benzyloximinocaproic and α-benzyloximinoisovaleric acids were prepared in 73 and 79% yields, respectively, from 3-benzyloximino-2-heptanone and 2-benzyloximino-1-methyl-3-pentanone. These acids were reduced to the corresponding α-amino acids without purification. In working up the α-benzyloximinoisovaleric acid in the usual manner, it was found that much of the sodium salt of this acid was extracted into the chloroform and ether used to remove unreacted starting material. Since it has been noted[4] that the sodium salt of α-benzyloximino-β-phenylpropionic acid is similarly soluble in organic solvents, it appears that this complication is one which should be anticipated whenever salts of α-alkoximino acids containing bulky organic groups are being processed.

The action of alkaline hypochlorite solutions on α-oximino ketones wherein the oxime group was not protected by alkylation led to an entirely different result from that found with the α-alkoximino ketones. Although a chloronitroso derivative similar to that obtained from simple oximes by the action of hypochlorite[5] was not the final product, it may have been an intermediate, since in a preliminary experiment a transient green color was noted when 3-oximino-2-heptanone was treated with sodium hypochlorite solution. In larger scale experiments using a 10% sodium hypochlorite solution containing excess base, 3-oximino-2-heptanone was converted to a mixture of about equal amounts of *n*-valeronitrile and *n*-valeric acid, and 1-oximino-1-phenyl-2-propanone gave benzoic acid in 86% yield. In the latter experiment, a strong odor of benzonitrile was noted at an intermediate stage. It thus appears that the action of hypohalite on α-oximino ketones leads in essence to a "second order" Beckmann rearrangement, followed by at least partial hydrolysis of the nitrile initially formed. This interesting reaction deserves further study, which was not possible when this investigation was carried out.

Although the reduction of α-alkoximino acids (step 4) was reported by previous workers to be difficult to carry out in good yield,[4] it was found in this study that the combination of ethanol solvent and palladium-on-charcoal catalyst gives essentially quantitative yields of amino acids from α-ethoximino acids when hydrogenation is carried out at moderate pressure (50 p.s.i.). Chemical reduction with metal and acid was also effective but far less convenient than hydrogenation. All reduction studies are summarized in Table IV.

TABLE IV

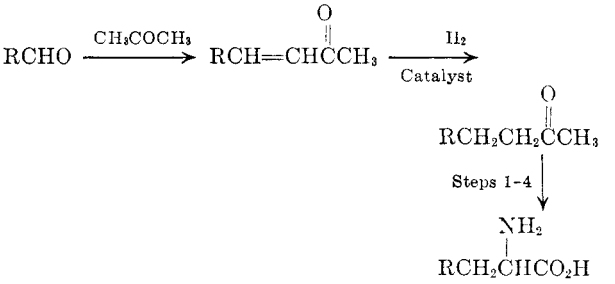
REDUCTION OF α-ALKOXIMINO ACIDS TO α-AMINO ACIDS



R	R′	Method[a]	Yield
$-(CH_2)_3CH_3$	$-CH_2CH_3$	A	85
		B	69
$-(CH_2)_3CH_3$	$-CH_2C_6H_5$[b]	A	21
		B	26
$-(CH_2)_3CH_3$	$-CH_2CH_2-$	A	93
$-CH(CH_3)_2$	$-CH_2CH_3$	A	91
$-CH(CH_3)_2$	$-CH_2C_6H_5$[b]	A	33
$-CH_3$	$-CH_2CH_3$	A	93
$-CH_3$	$-CH_2C_6H_5$	A	88
$-CH_2C_6H_5$	$-CH_2CH_3$	A	93

[a] A = Catalytic hydrogenation in ethanol over 5% palladium-on-charcoal. B = Chemical reduction with zinc and acetic acid. [b] Not purified before reduction.

As a method of preparing α-amino acids, the synthesis described herein is obviously of fairly general utility, since almost any ketone having a methyl group on one side of the carbonyl function and a methylene group on the other can be converted to an α-amino acid with loss of the methyl group. The new sequence deserves consideration as a substitute for the classical Erlenmeyer synthesis of amino acids, since the same aldehyde which is condensed with hippuric acid, hydantoin, thiohydantoin, diketopiperazine, or rhodanine in variants of the Erlenmeyer synthesis[6–8] may be condensed with acetone and converted to the desired α-amino acid by the sequence shown below:



(5) O. Piloty, *Ber.*, **31**, 452 (1898).

(6) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd Ed., Reinhold Publishing Corp., New York, 1956, p. 434.

(7) H. E. Carter, *Org. Reactions*, **III**, 218 (1946).

(8) H. Gilman, *Organic Chemistry*, **Vol. 2**, 2nd Ed., John Wiley and Sons, Inc., New York, 1943, p. 1107.

In the only case where a direct comparison is possible, the conversion of benzaldehyde to phenylalanine, combination of the data presented here with that of others[9,10] gives a calculated overall yield of 37% for the new sequence, not greatly different from the 39–43% reported[11] for the Erlenmeyer azlactone synthesis. Since the new sequence involves more steps than the Erlenmeyer procedure, it probably will be preferred only when it is desired to take advantage of the virtues of the intermediate α-alkoximino acid. As pointed out by Waters and Hartung,[4] the potential amino group in this intermediate is present in a chemically rather inert structure, so that chemical modification of the carboxyl function, as in the preparation of intermediates for peptide formation and in peptide formation itself, can be carried out. When the desired modification has been achieved, conversion of the alkoximino group to the amino group can be carried out under very mild reduction conditions.

EXPERIMENTAL[12]

Not all experiments reported in the tables are described below, but examples of all techniques used are given.

3-Oximino-2-heptanone. Into 800 ml. of ether containing 207.4 g. (1.814 moles) of 2-heptanone and 23 ml. of concentrated hydrochloric acid was passed methyl nitrite, generated from 82.6 g. (2.58 moles) of methanol, 165.9 g. (2.28 moles) of 95% sodium nitrite in 100 ml. of water, and 160 ml. (2.86 moles) of concentrated sulfuric acid diluted with 145 ml. of water. The reaction temperature rose spontaneously to 39° and was held there by refluxing ether. Addition of the methyl nitrite required about 2 hr. When all had been added, the reaction mixture was stirred for 20 min., and then a solution of 33.6 g. of sodium bicarbonate in 400 ml. of water was added cautiously. When gas evolution had ceased, the aqueous layer was separated and washed with 100 ml. of ether. The combined ether solution was dried over anhydrous magnesium sulfate. Evaporation of the ether left 244.0 g. (94%) of crude 3-oximino-2-heptanone. Recrystallization from carbon tetrachloride gave 176.3 g. (68%) of pure white crystals, m.p. 59–60°.

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 9.25; N, 9.77.

2-Ethoximino-1-phenyl-3-butanone. Into a solution of 148.2 g. (1.00 mole) of 1-phenyl-3-butanone and 12 ml. of concentrated hydrochloric acid in 400 ml. of ether was passed the methyl nitrite generated by adding a solution of 33.4 ml. (0.60 mole) of concentrated sulfuric acid in 60 ml. of water to a mixture of 35.2 g. (1.10 moles) of methanol, 76.4 g. (1.05 moles) of sodium nitrite, and 50 ml. of water. About 4.5 hr. were required for the addition, the temperature being maintained at 33–38° by refluxing ether. When addition was complete, the mixture was stirred for 30 min., then cooled to 17°. A solution of 60 g. (1.50 moles) of sodium hydroxide in 250 ml. of water was added over 10 min., the temperature being kept below 20° by external cooling. This mixture was stirred for 30 min., and then the basic oxime solution was separated from the ether layer. The basic solution was heated to 70°, and 185.0 g. (1.20 moles) of ethyl sulfate and a solution of 48.0 g. (1.20 moles) of sodium hydroxide in 160 ml. of water were added simultaneously over 30 min. Heat of reaction maintained the temperature at 70–75°. At the end of this time heat was applied, and the mixture was held at 70–75° for an hour. Then the mixture, which had separated into two layers, was cooled to room temperature, and the organic layer was separated. The aqueous layer was extracted with three 200-ml. portions of ether, and the ether extracts combined with the organic layer were dried over anhydrous magnesium sulfate. Evaporation of the ether left 166.2 g. (81%) of crude 2-ethoximino-1-phenyl-3-butanone. Distillation at reduced pressure gave 157.2 g. (77%) of pure material, b.p. 73–75° (0.18 mm.), n_D^{35} 1.5069.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.42; H, 7.48; N, 6.95.

O,O′-Ethylenebis(3-oximino-2-heptanone). To a solution of 12.0 g. (0.30 mole) of sodium hydroxide in 15 ml. of water and 150 ml. of methanol was added 42.9 g. (0.30 mole) of 3-oximino-2-heptanone. The oxime dissolved to give an orange-brown solution. Then 18.8 g. (0.10 mole) of ethylene dibromide was added, and the solution was allowed to stand for several days in a tightly stoppered bottle. At the end of this time the methanol was evaporated under reduced pressure, and 100 ml. of water was added to the pasty residue. A liquid organic layer separated, and was extracted into three 100-ml. portions of ether. The combined ether layer was washed with three 50-ml. portions of 10% sodium hydroxide solution, and then was dried over anhydrous magnesium sulfate. Acidification of the combined original water layer and basic washes led to the recovery of 18.2 g. (0.127 mole) of 3-oximino-2-heptanone. Evaporation of the ether from the liquid organic product left 23.3 g. of orange oil. Distillation under reduced pressure gave 18.2 g. (58%) of O,O′-ethylenebis(3-oximino-2-heptanone), b.p. 133–135° (0.55 mm.), n_D^{35} 1.4630.

Anal. Calcd. for $C_{16}H_{29}O_4N_2$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.40; H, 9.14; N, 9.03.

2-Ethoximinocaproic acid. To 639 g. of a 5.25% sodium hypochlorite solution (containing 0.45 mole of sodium hypochlorite) was added 17.1 g. (0.10 mole) of 3-ethoximino-2-heptanone and 50 ml. of dioxane. The solution was heated to 90° with stirring, and was held at 90–96° for 20 min. while chloroform, water, and dioxane distilled out slowly. The resulting clear solution was cooled to room temperature and tested for excess hypochlorite with acidified potassium iodide solution. A positive test (brown color) was obtained, and the solution was treated with solid sodium bisulfite until the test was negative. The solution was then acidified with 5*N* sulfuric acid. An oil separated, and was extracted into three 100-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the residue was distilled under reduced pressure to give 13.1 g. (76%) of 2-ethoximinocaproic acid, b.p. 67–69° (0.4 mm.), n_D^{35} 1.4487. Redistillation of part of the product gave b.p. 65–67° (0.4 mm.), n_D^{35} 1.4510.

Anal. Calcd. for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 8.09; Neut. equiv., 173.2. Found: C, 55.31; H, 8.60; N, 8.04; Neut. equiv., 173.4.

2-Ethoximino-3-methylbutyric acid. A solution of 80.0 g. (2.0 moles) of sodium hydroxide in 600 ml. of water was cooled to −4°, and 56.7 g. (0.80 mole) of liquid chlorine was added dropwise with stirring, keeping the temperature below 0°. To the resulting solution was added 100 ml. of dioxane, and (rapidly) 31.4 g. (0.20 mole) of 3-ethoximino-4-methyl-2-pentanone. Over about 40 min., the temperature rose spontaneously to 52° and then dropped off slowly. When the mixture had cooled to room temperature, it was tested for unreacted hypochlorite (negative) and then was acidified with 120 ml. of 5*N* sulfuric acid. The oil which separated was extracted into three 150-ml. portions of ether, and the ether solution was dried over anhydrous magnesium sulfate. The ether was evaporated, and the residue was

(9) N. L. Drake and P. Allen, Jr., *Org. Syntheses*, **Coll. Vol. I**, 2nd Ed., 77 (1941).

(10) L. W. Covert, R. Connor, and H. Adkins, *J. Am. Chem. Soc.*, **54**, 1658 (1932).

(11) Ref. 6, p. 437.

(12) All boiling points and melting points are uncorrected.

distilled under reduced pressure to give 23.5 g. (74%) of 2-ethoximino-3-methylbutyric acid, b.p. 62–64° (0.9 mm.), n_D^{35} 1.4436. Part of the material on redistillation gave b.p. 53–53.5° (0.5 mm.), n_D^{35} 1.4432.

Anal. Calcd. for $C_7H_{13}O_3N$: C, 52.80; H, 8.23; N, 8.80; Neut. equiv., 159.2. Found: C, 52.84; H, 8.12; N, 8.97; Neut. equiv., 161.1.

DL-*Phenylalanine.* A solution of 10.4 g. (0.05 mole) of 2-ethoximino-3-phenylpropionic acid in 50 ml. of absolute ethanol was placed in the reaction bottle of a Parr Pressure Reaction Apparatus, Type 3911. The bottle was flushed with nitrogen, and 3.0 g. of a commercial 5% palladium-on-charcoal catalyst was added. The bottle was placed in the apparatus, evacuated, pressurized with hydrogen to 50 p.s.i., heated to 50°, and agitated until the theoretical amount of hydrogen had been taken up. This required 3 hr. The reduction mixture was cooled to 0° and filtered by suction. The recovered solid (catalyst and most of the product) was boiled for 10 min. with 250 ml. of water, and the mixture was filtered hot. The undissolved solid (catalyst) was washed on the filter with three 30-ml. portions of boiling water. The combined aqueous filtrate was concentrated to 175 ml. and cooled in ice. The first crop of DL-phenylalanine crystallized and was recovered by filtration and dried. It amounted to 5.0 g. Further concentration of the filtrate, followed by crystallization and recovery, gave an additional 2.7 g. of product. The total recovery was thus 7.7 g. (93%). The infrared spectrum of this product was identical with that of an authentic specimen of DL-phenylalanine.

DL-*Norleucine.* A solution of 7.3 g. (0.10 mole) of 2-ethoximinocaproic acid in 300 ml. of glacial acetic acid was heated to 100°, the heat was removed, and 65.4 g. (1.0 mole) of zinc powder was added over 30 min. at such a rate that the temperature was held at 95–101°. External heating was then applied, and the temperature was held at 95–101° for 1 hr. At the end of this time, 150 ml. of acetic acid was distilled off under reduced pressure, and the residue was taken up in a liter of water. The suspended solid was removed by filtration, and hydrogen sulfide gas was passed into the filtrate until no further zinc sulfide precipitated. The zinc sulfide was removed by filtration, and the filtrate was concentrated to 250 ml. A precipitate began to form, and more appeared when the mixture was cooled to 2° and brought to *p*H 3.5 with about 5 ml. of 10% aqueous sodium hydroxide. The white crystals of DL-norleucine, after recovery by filtration and drying, amounted to 7.1 g. More product, amounting to 1.9 g., was recovered by extracting the solids originally recovered from the reduction mixture with 150 ml. of boiling water, treating with hydrogen sulfide to precipitate zinc sulfide, removing the precipitate by filtration, and concentrating. The total yield of DL-norleucine was thus 9.0 g. (69%). The infrared spectrum of this product was identical to that of authentic DL-norleucine.

Action of sodium hypochlorite on 3-oximino-2-heptanone. A solution of 80.0 g. (2.0 moles) of sodium hydroxide in 600 ml. of water was cooled to −5°, and 56.7 g. (0.80 mole) of liquid chlorine was added dropwise with stirring, the temperature being held between −5 and 0°. The solution was then warmed to 26°, and the addition of 28.6 g. (0.20 mole) of 3-oximino-2-heptanone was begun. The temperature rose rapidly and after 10 min. and addition of about a third of the oxime it has reached 75°. Cooling was applied, and the rest of the oxime was added over 20 min. with the temperature held at 72–76°. The mixture was allowed to cool slowly to 29° over 4 hr., at which point a test for unreacted hypochlorite was negative. A small amount of organic liquid had separated, and this was extracted into three 100-ml. portions of ether. The aqueous solution was then cooled in ice and acidified with concentrated hydrochloric acid. The organic layer which separated was extracted into three 100-ml. portions of ether. Both ether solutions were dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue from the extraction of the basic solution amounted to 7.1 g. On the basis of its infrared spectrum, it appeared to be largely *n*-valeronitrile. The residue from the extraction of the acidic solution amounted to 15.3 g., and appeared on the basis of infrared spectrum to be largely *n*-valeric acid. Distillation of this material under reduced pressure gave 8.4 g. of fairly pure *n*-valeric acid, b.p. 80–84° (10 mm.), n_D^{35} 1.4038. Authentic *n*-valeric acid gave n_D^{35} 1.4024.

Action of sodium hypochlorite on 1-oximino-1-phenyl 2-propanone. To a solution of sodium hypochlorite prepared as described above was added 32.6 g. (0.20 mole) of 1-oximino-1-phenyl-2-propanone over 45 min. The temperature was held at 22–29° by external cooling. A strong odor of benzonitrile was noted as the reaction progressed. When the oxime had all been added, the mixture was stirred for 30 min. at 22–26°, at the end of which time some solid remained undissolved. A test for hypochlorite was positive, and the remaining hypochlorite was destroyed by adding solid sodium bisulfite. The mixture was then extracted with four 100-ml. portions of ether, the solid passing into solution. The ether solution was dried over anhydrous magnesium sulfate, and the ether was evaporated under reduced pressure. There was obtained 9.7 g. of white solid, shown by infrared spectrum to be unchanged starting material. The aqueous solution remaining after the extraction was cooled in ice and acidified with concentrated hydrochloric acid. A heavy white precipitate came down. It was recovered by suction filtration, washed with two 50-ml. portions of cold water, sucked as dry as possible, and finally dried under vacuum. There was obtained 14.7 g. (86%, based on starting material not recovered) of benzoic acid, m.p. 121–122°. A mixture with authentic benzoic acid gave m.p. 122.5–124°.

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