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The Reaction of Halogenated Biacetyl Monoximes with Esters of Amino Acids

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1-Chloro-2-oximino-3-butanone (I) was prepared by the nitrosation of chloroethyl methyl ketone with an alkyl nitrite. I was treated with the L-leucine ethyl ester (II) to give 2-(2-oximino-3-oxobutylamino)-4-methylvalerate (III) and 2-[*N*, *N*-bis(2-oximino-3-oxobutyl)amino]-4-methylvalerate (IV). In a similar manner, 1-bromo-3-oximino-2-butanone (V) was treated with II to give 2-(3-oximino-2-oxobutylamino)-4-methylvalerate (VI). The reaction of the carbonyl group of III and VI with hydroxylamine and hydrazine was also studied. The treatment of VI with ammonia gave 6-(2-oximinoethyl)-3-isobutyl-2-hydroxypyrazine. Reactions of I and V with other esters of amino acids were also carried out.

It has been shown in our laboratory[1] that the reaction of α-haloximes with amino acid derivatives gives *N*-(2-oximinoalkyl)amino acid derivatives in good yields and that it is useful for synthesizing 2-hydroxypyrazines. In the present research this reaction was further studied by using monohalogenated biacetyl monoximes, in which a reactive carbonyl group is present besides a halogen atom.

Recently, Ogloblin has prepared 1-chloro-2-oximino-3-butanone (I) by treating methyl vinyl ketone with nitrosyl chloride and showed that the reaction of I with hydroxylamine hydrochloride or phenylhydrazine yielded the corresponding carbonyl derivatives, while I reacted with diethylamine to give 1-diethylamino-2, 3-butanedione-2-oxime.[2] However, it has not yet been clarified in the reaction of I with primary amines whether the carbonyl group is condensed or the chlorine atom is displaced.

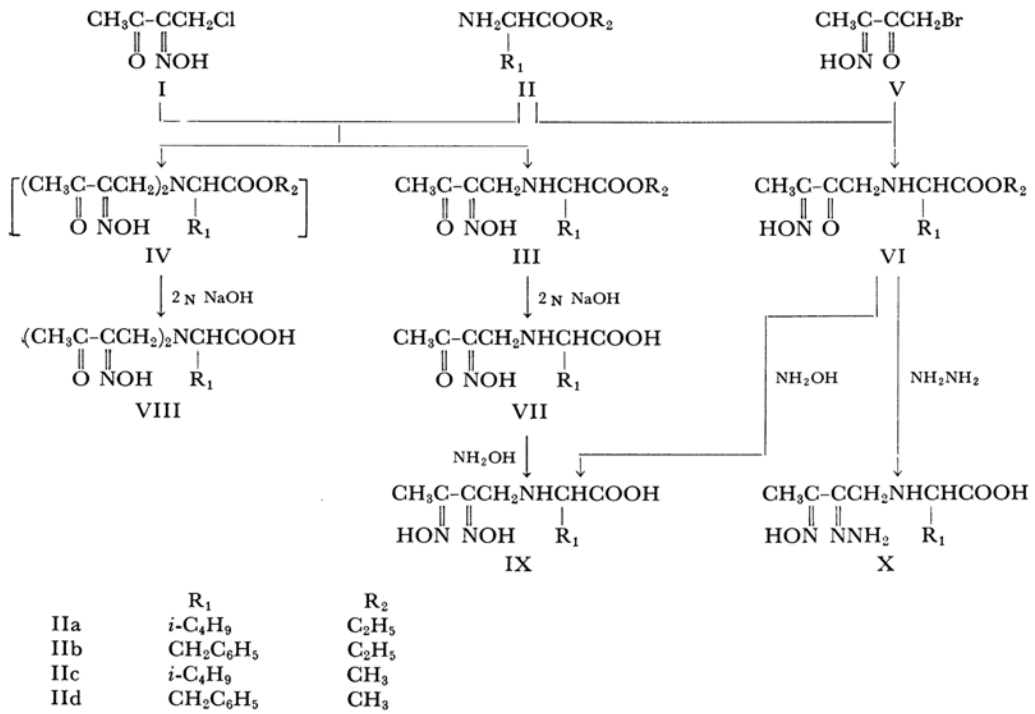
1-Chloro-2-oximino-3-butanone (I) was prepared by a more convenient method than Ogloblin's: the chloroethyl methyl ketone obtained from acetyl chloride and ethylene[3] was treated with an alkyl nitrite to give I in a good yield.

When I was treated with two mole equivalents of the L-leucine ethyl ester (IIa) in an ethereal solution, one mole equivalent of hydrochloride of IIa separated immediately, and ethyl 2-(2-oximino-3-oxobutylamino)-4-methylvalerate (IIIa) was obtained in a 44% yield, while there was also a 38% yield of ethyl 2-[*N*, *N*-bis(2-oximino-3-oxobutyl)amino]-4-methylvalerate (IVa). Both products were characterized by hydrolysis with 2 N sodium hydroxide to the corresponding acids (VIIa and VIIIa). The infrared spectrum of IIIa showed strong absorption bands at 1730 ($COOC_2H_5$) and 1685 cm^{-1} (C=O conjugated with C=N). The acid (VIIa) was treated with hydroxylamine in an alkaline solution to give 2-(2, 3-dioximinobutylamino)-4-methylvaleric acid (IXa). When I was treated with the DL-phenylalanine ethyl ester (IIb) in the same manner as in the case of IIa, ethyl 2-(2-oximino-3-oxobutylamino)-3-phenylpropionate (IIIb) was obtained.

From the above facts, it became clear that, in the reaction of I with esters of amino acids, condensation with the carbonyl group did not occur, but the chlorine atom was exclusively displaced. The reaction of 1-bromo-3-oximino-2-butanone (V)[4] with the ester of amino acids was then attempted, though the reactions of α-halo ketones with primary amines have been known to be generally very complex.[5] There has been no report about the reaction of V except with thioformamide or thiobenzamide.[6]

When V was treated with piperidine in an ethereal solution, 1-piperidino-3-oximino-2-butanone was obtained in a good yield. The treatment of V with the L-leucine ethyl ester (IIa) in an ethereal solution gave the expected ethyl 2-(3-oximino-2-oxobutylamino)-4-methylvalerate (VIa) in a 46% yield. In the same manner, V reacted with other esters of amino acids to yield *N*-(3-oximino-2-oxobutyl)amino acid esters (VI) (Fig. 1). VI was characterized by a study of its infrared spectrum, in which strong absorption bands at 1720

1) M. Masaki and M. Ohta, This Bulletin, **36**, 922, 1177 (1963).
2) K. A. Ogloblin and A. A. Potekhin, *Zh. Obshch. Khim.*, **34**, 2688 (1964); *Chem. Abstr.*, **61**, 14519 (1964).
3) F. Sondheimer and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5438 (1953).
4) M. P. Doerner, U. S. Pat. 2821555 (1958); *Chem. Abstr.*, **52**, 9198 (1958).
5) C. L. Stevens, P. Blumbergs and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).
6) H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **23**, 197 (1940); A. Silberg and A. Benkeo, *Chem. Ber.*, **97**, 1915 (1964).

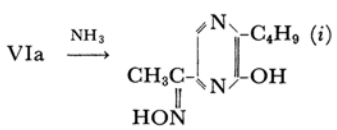


	R_1	R_2
IIa	i-C_4H_9	C_2H_5
IIb	$CH_2C_6H_5$	C_2H_5
IIc	i-C_4H_9	CH_3
IId	$CH_2C_6H_5$	CH_3

Fig. 1.

$(COOR_2)$ and 1685 cm^{-1} (C=O) appeared, as well as by the reactions described below. VIa was converted to IXa by treatment with hydroxylamine, followed by the hydrolysis of the oily product in an aqueous alkali; VId gave 2-(2-hydrazono-3-oximinobutylamino)-3-phenylpropionic acid (Xd) when treated with hydrazine hydrate and then subjected to hydrolysis.

When VIa was treated with ammonia in methanol, 6-(2-oximinoethyl)-3-isobutyl-2-hydroxypyrazine was obtained in a poor yield.



Experimental

1-Chloro-2-oximino-3-butanone (I). — 4-Chloro-2-butanone was prepared from acetyl chloride and ethylene according to Sondheimer's method.[3] Into a solution of 4-chloro-2-butanone (64 g.) in absolute ether (300 ml.), hydrogen chloride was introduced at the rate of 3—5 bubbles a second. The gaseous ethyl nitrite (1.5 mole equivalent) [prepared from sodium nitrite (55.2 g.), ethanol (36.8 g.), and sulfuric acid (39.2 g.)] was introduced with vigorous stirring into the solution at 30—35°C during a six-hour period. After all the ethyl nitrite had passed in, the stirring and the addition of hydrogen chloride were continued for an additional thirty minutes. The ethereal solution was then treated with activated charcoal and concentrated under reduced pressure to give a brown crystalline product, which was washed with carbon tetrachloride to yield I (43 g., 53%). The product was sufficiently pure for further experiments. A part of the product was recrystallized twice from benzene into the form of colorless plates, m. p. 92—93°C (lit.[2] 89—90°C).

The Reaction of I with L-Leucine Ethyl Ester (IIa).—To a solution of the L-leucine ethyl ester (IIa, 7 g.) in absolute ether (30 ml.), I (3 g.) was added with ice-cooling. Hydrochloride of the ester (IIa) separated immediately. The mixture was then allowed to stand at room temperature overnight. The hydrochloride (4.3 g.) was filtered off and washed with ether. The combined ethereal solution was extracted with 130 ml. (50+50+30 ml.) of 1 N hydrochloric acid. The aqueous extract was neutralized with sodium carbonate until pH 3, thus separating a small quantity of an oil, which was removed by extracting with ether. The aqueous layer was further neutralized with sodium carbonate to pH 6 to give ethyl 2-(2-oximino-3-oxobutylamino)-4-methylvalerate (IIIa; 2.5 g.; 44%, calculated on I). Two recrystallizations from *n*-hexane gave colorless needles, m. p. 96.5—97.5°C.

Found: C, 55.98; H, 8.82; N, 11.00. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58; N, 10.85%.

The combined ethereal layer and extract were dried over anhydrous sodium sulfate and concentrated to give an oily product (1.9 g.), which was then dissolved in 2 N sodium hydroxide (20 ml.) and allowed to stand at room temperature overnight. After being diluted with water (40 ml.) and treated with activated charcoal, the solution was neutralized with 4 N acetic acid to give 2-[*N*, *N*-bis(2-oximino-3-oxobutyl)amino]-4-methylvaleric acid (VIIIa; 1.4 g.; 38%, calculated on I), which was then recrystallized twice from 50% aqueous

dimethylformamide into the form of colorless prisms, m. p. 171—172°C.

Found: C, 50.66; H, 6.97; N, 12.66. Calcd. for $C_{14}H_{23}N_3O_6$: C, 51.05; H, 7.04; N, 12.76%.

2-(2-Oximino-3-oxobutylamino)-4-methylvaleric Acid (VIIa).—In 2 N sodium hydroxide (10 ml.) IIIa (0.46 g.) was dissolved; the resultant solution was allowed to stand at room temperature overnight. The solution was treated with activated charcoal, and then neutralized with 4 N acetic acid to afford a product (0.35 g., 85%) which was then recrystallized from dimethylformamide into the form of colorless prisms, m. p. 230°C (decomp.).

Found: C, 52.43; H, 7.91. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88%.

Ethyl 2-(2-Oximino-3-oxobutylamino)-3-phenylpropionate (IIIb).—To a solution of the DL-phenylalanine ethyl ester (IIb, 12.6 g.) in absolute ether (150 ml.), I (4.2 g.) was added with ice-cooling; the mixture was then allowed to stand at room temperature overnight. After the precipitate (6.8 g.) had been removed from the mixture, the filtrate was allowed to stand in a refrigerator to separate crystals gradually. After three hours the crystals (3.1 g.) were collected, and the filtrate was washed with water and extracted with 1 N hydrochloric acid. The acidic extract was treated with activated charcoal and neutralized with sodium carbonate until pH 6 to give the product (1.9 g.). The total yield was 5 g. (55%). An analytical sample was obtained, by recrystallization from ethyl acetate, as colorless needles, m. p. 119—120°C.

Found: C, 61.87; H, 7.03; N, 9.69. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58.%

2-(2, 3-Dioximinobutylamino)-4-methylvaleric Acid (IXa).—To a solution of VIIa (1.9 g.) in 1 N sodium hydroxide (30 ml.) hydroxylamine hydrochloride (0.8 g.) was added. After the resultant solution had been allowed to stand at room temperature for two days, it was treated with activated charcoal and acidified with 20% aqueous acetic acid to give IXa (1.9 g., 94%), which was then recrystallized from dimethyl formamide into the form of colorless prisms, m. p. 257—258°C.

Found: N, 17.04. Calcd. for $C_{10}H_{19}N_3O_4$: N, 17.13%.

1-Bromo-3-oximino-2-butanone (V).—This compound was prepared from bromobiacetyl and hydroxylamine according to Doerner's method.[4] Colorless plates; m. p. 85—86°C (lit.[4] 86—87°C).

1-Piperidino-3-oximino-2-butanone.—To a solution of piperidine (1.7 g.) in absolute ether (70 ml.) V (1.8 g.) was added, after which the mixture was allowed to stand at room temperature for three hours. The precipitate was then collected by filtration and washed with water in order to remove the hydrobromide of piperidine, thus obtaining a product (1.1 g.). The above ethereal filtrate was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crystalline product (0.4 g.). The total yield was 1.5 g. (82%). Recrystallization from ethyl acetate gave colorless needles, m. p. 135°C (decomp.).

Found: N, 15.28. Calcd. for $C_9H_{16}N_2O_2$: N, 15.21%.

Ethyl 2-(3-Oximino-2-oxobutylamino)-4-methylvalerate (VIa).—The following experiment was typical of the procedures used for the reaction of V with amino acid esters (II).

To a solution of the L-leucine ethyl ester (IIa, 12.7 g., 0.08 mole) in absolute ether (150 ml.), V (7.2 g., 0.04 mole) was added, the mixture was then allowed to stand at room temperature overnight. The precipitate was collected by filtration and washed with water, and the collected crystals were treated with water, in order to remove the hydrobromide; this yielded the product (1.3 g.). After being washed with water and dried over anhydrous sodium sulfate, the combined ethereal filtrate and washing were concentrated under reduced pressure. The crystalline residue was dissolved in carbon tetrachloride in order to filter it, thus giving VIa (3.4 g.). The total yield was 4.7 g. (46%); an analytical sample was obtained, by recrystallization from carbon tetrachloride, as colorless needles, m. p. 124.5—125.5°C (decomp.).

Found: C, 55.85; H, 8.34; N, 11.07. Calcd. for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58; N, 10.85%.

Ethyl 2-(3-Oximino-2-oxobutylamino)-3-phenylpropionate (VIb).—This ester was obtained from V (3.9 g.) and the DL-phenylalanine ethyl ester (IIb, 8.4 g.) in a 51% yield. Recrystallization from ethanol gave colorless needles, m. p. 121—122°C (decomp.).

Found: C, 61.58; H, 6.96; N, 9.63. Calcd. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58%.

Methly 2-(3-Oximino-2-oxobutylamino)-4-methylvalerate (VIc). — This ester was obtained from V (14.4 g.) and the L-leucine methyl ester (IIc, 23 g.) in a 40% yield. Recrystallization from methanol gave colorless needles, m. p. 149°C (decomp.).

Found: C, 54.09; H, 8.40; N, 11.62. Calcd. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47%.

Methyl 2-(3-Oximino-2-oxobutylamino)-3-phenylpropionate (VId).—This ester was obtained from V (7.2 g.) and the DL-phenylalanine methyl ester (IId, 14.3 g.) in a 40% yield. Recrystallization from ethanol gave colorless needles, m. p. 138—139°C (decomp.).

Found: C, 60.61; H, 6.82; N, 9.90. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07%.

The Reaction of VIc with Hydroxylamine.—To a solution of hydroxylamine [from hydroxylamine hydrochloride (0.43 g.) and sodium (0.15 g.) in methanol (20 ml.)], VIc (1.5 g.) was added; the suspension was warmed at 60—64°C for four hours and then allowed to stand at room temperature overnight. The resultant solution was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (10 ml.) and filtered. After the ethyl acetate had been removed under reduced pressure, the resultant brown oil was dissolved in 2 N sodium hydroxide (10 ml.) and allowed to stand at room temperature overnight. The alkaline solution was treated with activated charcoal and neutralized until pH 6 with 4 N acetic acid, thus obtaining crystals (0.55 g., 36%); these crystals were recrystallized from dimethylformamide into colorless prisms, m. p. 239.5°C (decomp.). The identity of this product with the IXa prepared from VIIa was confirmed by a mixed-melting-point determination and by a comparison of their infrared spectra.

2-(2-Hydrazono-3-oximinobutylamino)-3-phenylpropionic Acid (Xd).—To a suspension of VId (1 g.) in methanol (20 ml.) hydrazine hydrate (0.4 g.) was added, after which the suspension was refluxed for four hours. The resultant solution was concentrated

under reduced pressure, and the residual brown oil was dissolved in 2 N sodium hydroxide (10 ml.). After being allowed to stand at room temperature overnight, the solution was neutralized until pH 6 with 4 N acetic acid, thus giving yellowish crystals (0.4 g., 40%) which were recrystallized from dimethylformamide into the form of yellow prisms, m. p. 168—169°C (decomp.).

Found: N, 19.99. Calcd. for $C_{13}H_{18}N_4O_3$: N, 20.13%.

6-(2-Oximinoethyl)-3-isobutyl-2-hydroxypyrazine.—A suspension of VIa (4.8 g.) in methanol (100 ml.) was saturated with ammonia with ice-cooling and then allowed to stand at room temperature for two days. The resultant red solution was concentrated under reduced pressure to afford a red residue, which was dissolved in water (100 ml.) and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate, and then concentrated under reduced pressure to give a mixture of a yellow oil and crystals. The mixture was dissolved in ethyl acetate (2 ml.) for filtration, and the crystals (0.2 g., 5%) were recrystallized twice from ethyl acetate to give colorless needles, m. p. 200.5—201.5°C (decomp.).

λ_{max}^{EtOH} 245 mμ (ε=11100), 330 (10200), and 340 (10100, sh.).

Found: C, 57.63; H, 7.26; N, 20.29. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08%.