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The Reactions of 1-Chloro-2-oximino-3-butanone

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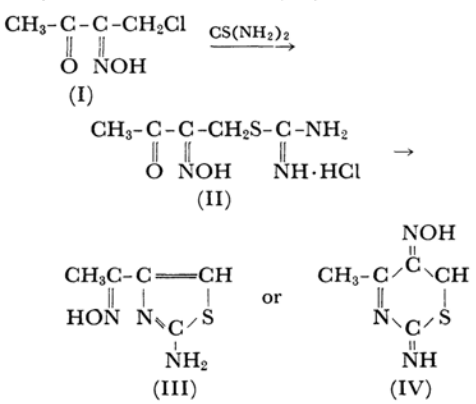
The reaction of 1-chloro-2-oximino-3-butanone (I) with thiourea at 50—60°C gave *S*-(2-oximino-3-oxobutyl)thioformamidine hydrochloride (II), which upon being heated in an aqueous solution, then gave 2-amino-4-(1-oximinoethyl)thiazole (III). The treatment of I with aminoacetonitrile gave a mixture of *N*-(2-oximino-3-oxobutyl)aminoacetonitrile (IV) and *N*, *N*-bis(2-oximino-3-oxobutyl)aminoacetonitrile (V), which were confirmed as the corresponding amidoxime and benzoyl or *p*-nitrobenzoyl derivatives respectively. The reaction of I or 3-chloro-2-oximinopropiophenone with barium thiocyanate gave the corresponding acyclic thiocyanates (VI), while the reaction of *anti*-bromoacetophenone oxime with barium thiocyanate yielded 2-amino-4-phenylthiazole-3-oxide. That the cyclization reaction between the oximino and the cyano groups of V or VI did not occur seemed to favor the *syn*-chloromethyl conformation of the oximino group in I, a mechanism for which is hereby proposed.

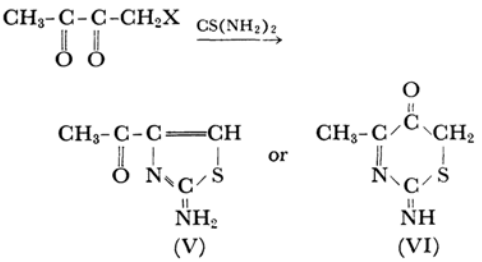
The reaction of halogenated biacetyl monooximes has received only scant attention, but they seem to be useful for some synthetic reactions because they have three functional groups. The reaction of 1-bromo-3-oximino-2-butanone with thioformamide or thiobenzamide has been known to give the corresponding thiazole derivatives.[1] Recently, Ogloblin and Potekhin reported the preparation of 1-chloro-2-oximino-3-butanone (I) and its reactions with hydroxylamine hydrochloride, phenylhydrazine, or diethylamine to give the corresponding carbonyl derivatives or substituted product.[2]

We have shown in a previous paper that the reaction of I with amino acid esters, as an example of primary amines, gave products formed not by the condensation of the carbonyl group, but by the displacement of chlorine in I.[3] In the present experiment, the reactions of I with thiourea, aminoacetonitrile, and barium thiocyanate were examined.

The reaction of I with thiourea in ethanol at 50—60°C gave *S*-(2-oximino-3-oxobutyl)thioformamidine hydrochloride (II), which was characterized by elementary analysis and by a study of the infrared spectrum of the free base. When II was boiled in an aqueous solution and then neutralized with ammonia, a crystalline product, m. p. 206—207°C, was obtained. The elementary analysis of the product indicated that the empirical formula, $C_5H_7N_3OS$, held, a formula compatible with the cyclic structure, 2-amino-4-(1-oximinoethyl)thiazole (III) or 2-imino-4-methyl-5-oximino-5, 6-dihydro-2*H*-1, 3-thiazine (IV).



Garreau reported the treatment of 1-chloro-2, 3-butanedione with thiourea to give a substance, m. p. 230°C, the structure of which he claimed to be 4-acetyl-2-aminothiazole (V), though the possibility of the thiazine structure (VI) could not be excluded.[4]



X=Cl or Br

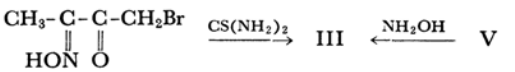
1) M. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **23**, 197 (1940); A. Silberg and A. Benkoe, *Chem. Ber.*, **97**, 1915 (1964).

2) K. A. Ogloblin and A. A. Potekhin, *J. Gen. Chem. USSR*, **34**, 2710 (1964).

3) M. Sugiyama, M. Masaki and M. Ohta, This Bulletin, submitted for publication.

4) Y. Garreau, *Chem. Zentr.*, **1947**, 731; *Chem. Abstr.*, **51**, 12148 (1957).

The substance, m. p. 230°C, prepared from 1-bromo-2, 3-butanedione and thiourea was treated with hydroxylamine to give the corresponding oxime, which was confirmed to be identical with the substance, m. p. 206—207°C obtained above. The identical product was also obtained directly by the reaction of 1-bromo-3-oximino-2-butanone with thiourea.



On the basis of these results, as well as infrared and ultraviolet spectral data, the substance with a m. p. of 206—207°C was concluded to be 2-amino-4-(1-oximinoethyl)thiazole (III); accordingly, the substance with a m. p. of 230°C, obtained from 1-bromo-2, 3-butanedione and thiourea, must be 4-acetyl-2-aminothiazole (V).

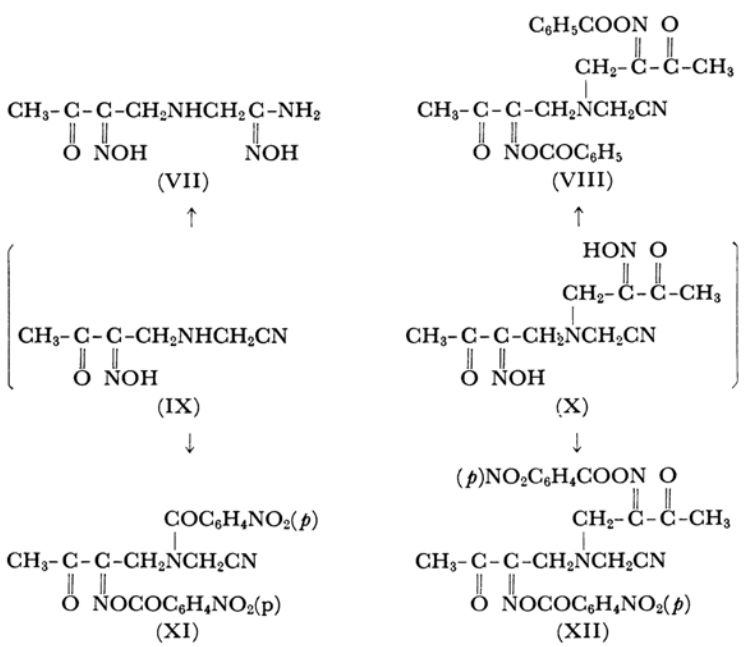
The infrared spectrum of III showed two absorption bands, at 3380 and 3305 cm^{-1}, which could be ascribed to asymmetric and symmetric NH_2-stretching vibrations, as the relationship of the wave numbers of the two bands accorded well with the equation of Bellamy-Williams.[5] The presence of the primary amine corresponded only with the III structure.

The ultraviolet spectrum of III showed two absorption maxima, at 224.5 and 270 mμ; this also supported the thiazole structure, since unsubstituted thiazole has an absorption maximum at 235 mμ[6] and the maximum bands of 2-amino-4-phenylthiazole were observed at 230.5 and 285 mμ.

A probable pathway for the formation of III from II would be the initial cyclization of II to give V and hydroxylamine, which then reacts to give III. A similar ring-closure by the loss of hydroxylamine was also observed in the reaction of bromoacetophenone oxime with thiourea; when bromoacetophenone oxime and thiourea were heated in an ethanolic solution for twenty minutes, 2-amino-4-phenylthiazole was obtained in a quantitative yield.

When I was treated with two equivalents of aminoacetonitrile in ethyl acetate at room temperature, an oily product was obtained with a quantitative amount of aminoacetonitrile hydrochloride. The oily product was soluble in water, and its purification was difficult. The treatment of the crude product with hydroxylamine afforded 2-(2-oximino-3-oxobutylamino)acetoamidoxime (VII), while treatment with benzoyl chloride gave *N*, *N*-bis(2-benzoyloximino-3-oxobutyl)amino acetonitrile (VIII). Thus, the oily product is probably a mixture of *N*-(2-oximino-3-oxobutyl)-aminoacetonitrile (IX) and *N*, *N*-bis(2-oximino-3-oxobutyl)aminoacetonitrile (X). Reaction with *p*-nitrobenzoyl chloride gave the corresponding di-*p*-nitrobenzoyl derivatives (XI, XII), from the yields of which the oily product appeared to include nearly equivalent amounts of IX and X (Scheme 1).

Sharp et al. described the reaction of α-oximino-



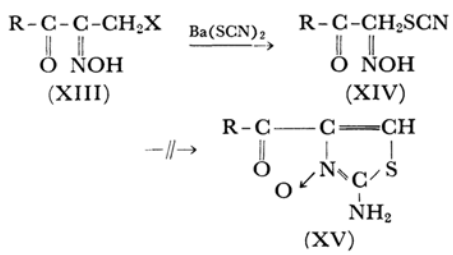
Scheme 1

5) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd, Methuen, London; John Wiley, New York (1958), p. 250.

6) A. R. Katritzky, "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York and London (1963), p. 59.

carbonyl compounds with α-aminonitrile to give 2-aminopyrazine-1-oxides.[7] The analogous ring closure between oximino and cyano groups of IX was attempted by treatment in the presence of acids or by the conversion of the nitrile into the iminoether, but the corresponding cyclic compound was not isolated.

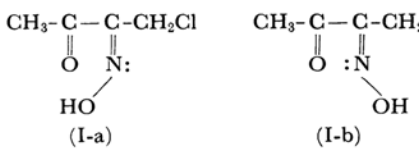
The reaction of 1-chloro-2-oximino-1-phenylpropane with barium thiocyanate has been reported to give 2-amino-4-methyl-5-phenylthiazole-3-oxide.[8] When 3-chloro-2-oximinopropiophenone (XIII, R=C_6H_5) was treated with barium thiocyanate, it gave not the corresponding cyclic compound (XV), but 2-oximino-3-oxo-3-phenylpropyl thiocyanate (XIV, R=C_6H_5), which was characterized by elementary analysis and by the presence of absorption bands near 2130 cm^{-1} (-SCN) in the infrared spectrum as well as by the negative ferric chloride reaction. The treatment of I with barium thiocyanate gave an oily product, which also had absorption bands near 2130 cm^{-1} in the infrared spectrum and did not show a color reaction with ferric chloride.



(XIII) (XIV) (XV)

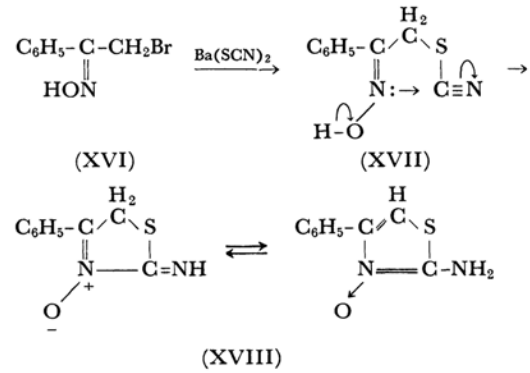
R=C_6H_5, CH_3

Although, in the case of the synthesis of aminopyrazine oxide[7] or aminothiazole oxide[8], neither the configuration of the oximes nor the mechanism of the cyclization reactions has been discussed, the pathways of those cyclization reactions probably involve an attack by the nitrogen of the oximino group on the carbon of the cyano group (see XVII). Therefore, if the hydroxyl group in the oxime of I has an *anti*-configuration to the chloromethyl group (I-a), IX or XIV may be expected to undergo ring closure readily, while if both groups are situated in the *syn*-configuration (I-b), the cyclization reaction of IX or XIV would not easily take place.



(I-a) (I-b)

When *anti*-bromoacetophenone oxime (XVI) was treated with barium thiocyanate, the cyclization reaction occurred expectedly, and 2-amino-4-phenylthizaole-3-oxide (XVIII), which shows a positive ferric chloride reaction, was obtained.



(XVI) (XVII)

(XVIII)

Thus, the fact that the cyclization reaction of IX or XIV did not occur may be ascribed to the *syn*-chloromethyl configuration (I-b) of the oxime in I.[9]

Experimental

S-(2-Oximino-3-oxobutyl)thioformamidine (The Free Base of II).—A mixture of thiourea (1.5 g.) and I (2.7 g.) in ethanol (40 ml.) was heated at 50—60°C for 2 hr. and then left standing at room temperature overnight. The solution was evaporated under reduced pressure to give an oily residue, which was the hydrochloride (II). The oily residue (II) was dissolved in water (40 ml.) and treated with activated charcoal. A half of the solution was neutralized with sodium bicarbonate (1.7 g.) to separate yellow crystals (2.7 g.). (The remaining half of the solution was used for the cyclization reaction in the next section.) The product (1 g.) was dissolved in 0.5 N hydrochloric acid (15 ml.), treated with activated charcoal, and then reprecipitated by neutralizing it with a clear aqueous solution of sodium bicarbonate (0.6 g. in 9 ml. of water). After it had been washed twice with water and twice with ethanol, it was analyzed. Fine yellow crystals; m. p. 128—130°C (decomp.). IR: ν_{max}^{KBr} 3300 (-NH-), 3000—2200 (broad band), and 1650 cm^{-1} (-C=O).

Found: C, 34.91; H, 5.05; N, 24.12. Calcd. for $C_5H_9N_3O_2S$: C, 34.28; H, 5.18; N, 23.99%.

2-Amino-4-(1-oximinoethyl)thiazole (III).—*a) From II.*—The remaining half of the solution of II described above was heated on a boiling water bath for 3 hr. After it had then cooled to room temperature, the solution was neutralized with an aqueous ammonia to separate almost colorless crystals, which were recrystallized twice from water by using activated charcoal. Colorless needles; m. p. 205—206°C. The product showed no depression in mixing tests with the specimen obtained by either the b) or the c) method. UV: λ_{max}^{EtOH} 224.5 mμ (ε=15700) and 270 (sh., 7700). IR:

7) W. Sharp and F. S. Spring, *J. Chem. Soc.*, **1951**, 932; J. J. Gallagher, G. T. Newbold, W. Sharp and F. S. Spring, ibid., **1952**, 4870.

8) A. Dornow, H. H. Marquardt and H. Paucksch, *Chem. Ber.*, **97**, 2165 (1964).

9) The *syn*-chloromethyl conformation of I might be supported by the fact that the melting point of 1-diethylamino-2, 3-butanedione-2-oxime[2] derived from I is essentially identical with that of authentic *syn*-1-diethylamino-2, 3-butanedione-2-oxime.[10]

10) G. B. Bachman and D. E. Welton, *J. Org. Chem.*, **12**, 221 (1947).

ν_{max}^{KBr} 3380 (*asym*-NH_2), 3305 (*sym*-NH_2), and 1650 cm^{-1} (-C=O).

Found: C, 38.86; H, 4.55; N, 26.93. Calcd. for $C_5H_7N_3OS$: C, 38.22; H, 4.49; N, 26.74%.

b) From 4-Acetyl-2-aminothiazole.—When thiourea (1.9 g.) was added to a solution of 1-bromo-2, 3-butanedione (4.2 g.) in ethanol (20 ml.), the mixture became a clear solution with an exothermic reaction; then colorless crystals soon separated. The resultant mixture was heated under reflux for 30 min. The crystals were collected and recrystallized from water to yield 4-acetyl-2-aminothiazole hydrobromide as colorless needles; m. p. 248—250°C (decomp.). (Found: N, 12.24%). The treatment of the hydrobromide with aqueous sodium bicarbonate gave the free base with a m. p. of 229—231°C (decomp.) (lit.[4] 230°C). A solution of the free base (0.95 g.), hydroxylamine hydrochloride (0.5 g.), and potassium hydroxide (0.4 g.) in methanol (50 ml.) was heated under reflux for 4 hr., after which the solvent was removed under reduced pressure; the residual solid was recrystallized twice from water and once from *n*-butanol to give 0.5 g. of colorless needles; m. p. 207—208°C.

c) From 1-Bromo-3-oximino-2-butanone. — Thiourea (0.76 g.) was added to a solution of 1-bromo-3-oximino-2-butanone (1.8 g.) in ethanol (15 ml.). The mixture soon became a clear solution with exothermic reaction. The solution was heated under reflux for 30 min. and then cooled to room temperature to give a crystalline product. An aqueous solution of the product was treated with sodium bicarbonate to give colorless crystals (0.5 g.), which were recrystallized from the solvent described in a) and b) to give colorless needles; m. p. 206—207°C.

The Reaction of Phenacylbromide Oxime with Thiourea.—A mixture of phenacylbromide oxime (2.0 g.) and thiourea (0.75 g.) in ethanol (20 ml.) was heated on a boiling water bath for 20 min. and then allowed to stand at room temperature for 1 hr. After the solution had been concentrated under reduced pressure, the residue was treated with water. The crystals were washed successively with an aqueous solution of sodium bicarbonate and with water. Yield, 1.6 g. Recrystallization from ethanol gave colorless needles; m. p. 150—151°C (lit.[11] 151—152°C). UV: λ_{max}^{EtOH} 230.5 mμ (ε=22300) and 285 (7400).

The Reaction of I with Aminoacetonitrile.—To a solution of aminoacetonitrile (4.5 g., 0.08 mole) in ethyl acetate (70 ml.), I (5.4 g., 0.04 mole) was added. The solution was then allowed to stand at room temperature overnight. After the hydrochloride of aminoacetonitrile (3.7 g.; 94.6%) had been filtered off, the filtrate was evaporated under reduced pressure to give an oily product which was readily soluble in water and alcohol, but not in ether or benzene. In order to remove the impurities, the oily product dissolved in ethyl acetate was chromatographed on alumina. After elution with ethyl acetate, the elute was evaporated to give a reddish oil, "oily product A," which was used for the following reactions.

2-(2-Oximino-3-oxobutylamino)acetoamidoxime Hydrochloride (VII).—A solution of the oily product A (2 g.) and hydroxylamine (1 g.) in methanol (25 ml.) was allowed to stand at room temperature for two days. The solution was then evaporated under reduced pressure to give an oily product. A solution of the product in ethanol (20 ml.) was treated with dry hydrogen chloride and allowed to stand in a refrigerator overnight. The solvent was evaporated under reduced pressure, and the residual product was treated with activated charcoal in ethanol. Yield, 1.34 g. Recrystallization from ethanol-ether gave white crystals; m. p. 140°C (decomp). IR: ν_{max}^{KBr} 2900—2500 (broad band) and 1690 cm^{-1} (-C=O).

Found: C, 31.87; H, 5.65; N, 25.08. Calcd. for $C_6H_{13}N_4O_3Cl$: C, 32.04; H, 5.79; N, 24.92%.

***N*, *N*-Bis(2-benzoyloximino-3-oxobutyl)aminoacetonitrile (VIII).**—A solution of benzoyl chloride (4 g.) in ethyl acetate was slowly stirred at −10—−5°C into a solution of the oily product A (4.4 g.) and pyridine (2.25 g.) in ethyl acetate (100 ml.). After the addition was complete, stirring was continued at that temperature two more hours. The solution was then washed with water, an aqueous solution of sodium bicarbonate, and again with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The oily product was treated with isopropyl alcohol (20 ml.) to give a crystalline product (1 g.). Several recrystallizations from isopropyl alcohol gave *N*, *N*-bis(2-benzoyloximino-3-oxobutyl)aminoacetonitrile. Colorless needles; m. p. 140—141°C. IR: ν_{max}^{KBr} 1765 (-C=O), 1708 (-C=O), and 1230 cm^{-1} (-COO-).

Found: C, 62.28; H, 5.00; N, 12.29. Calcd. for $C_{24}H_{22}N_4O_6$: C, 62.33; H, 4.80; N, 12.12%.

The *p*-Nitrobenzoylation of the Product Derived from I and Aminoacetonitrile.—A solution of *p*-nitrobenzoyl chloride (7.4 g., 0.04 mole) in ethyl acetate (40 ml.) was stirred, drop by drop, at −10—−5°C into a solution of the oily product A, prepared from I (2.7 g., 0.02 mole), aminoacetonitrile (2.2 g., 0.04 mole), and pyridine (3.2 g.) in ethyl acetate (40 ml.). After the stirring had been continued at that temperature for 8 hr., the mixture was washed with water; thereby a crystalline product (1.5 g.) was separated. The recrystallization of the crystalline product from acetonitrile gave *N*-*p*-nitrobenzoyl-*N*-(2-*p*-nitrobenzoyloximino-3-oxobutyl)aminoacetonitrile (X) as fine yellowish needles; m. p. 187°C (decomp.). IR: ν_{max}^{KBr} 1770 (-COO-), 1710 (-C=O), 1655 (-CONH-), 1530 (-NO_2), 1350 (-NO_2), and 1230 cm^{-1} (-COO-).

Found: C, 53.03; H, 3.49; N, 5.65. Calcd. for $C_{20}H_{15}N_5O_8$: C, 52.98; H, 3.34; N, 15.45%.

The organic layer in the above reaction was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual product was then treated with activated charcoal in chloroform. After the chloroform had been evaporated under reduced pressure, the oily residue was crystallized by teatment with isopropyl alcohol. The crystalline product (1.5 g.) was repeatedly recrystallized from a mixture of acetonitrile and ethanol (7 : 3) to give *N*, *N*-bis(2-*p*-nitrobenzoyloximino-3-oxobutyl)aminoacetonitrile (XII) as yellowish needles; m. p. 162—163°C. IR: ν_{max}^{KBr} 1765 (-COO-), 1710 (-C=O), 1530 (-NO_2), 1350 (-NO_2), and 1230 cm^{-1} (-COO-).

Found: C, 52.50; H, 3.80; N, 15.49. Calcd. for $C_{24}H_{20}N_6O_{10}$: C, 52.17; H, 3.65; N, 15.21%.

3-Chloro-2-oximinopropiophenone (XIII).— The

11) R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).

procedure for the preparation of 3-chloropropiophenone was modified from the method of Matsumoto and Hata.[12] The main modification was that chloroform was used as the solvent instead of tetrachloroethane. In this case, 3-chloropropiophenone was directly obtained without the isolation of phenyl vinyl ketone.

Benzoyl chloride (422 g.; 3 mole) was added, with stirring and ice-cooling, to a mixture of aluminum chloride (414 g.; 3.1 mole) and absolute chloroform (1000 ml.). Ethylene was then introduced into the stirred mixture at such a rate that all was absorbed, the internal temperature being kept between 10—15°C for 40 hr. The reaction mixture was poured into a mixture of hydrochloric acid (426 ml.) and ice (2.3 kg.). The organic layer was washed successively with dilute hydrochloric acid, an aqueous solution of sodium carbonate, and water, and dried over anhydrous sodium sulfate. After the chloroform had been evaporated under reduced pressure, the residual crystalline product was washed with petroleum ether and treated with activated charcoal in benzene or ether to give 3-chloropropiophenone (213 g.). On the concentration of the washings of petroleum ether, an additional product (72 g.) was obtained. The total yield was 285 g. (56.4%); m. p. 46—47°C (lit. 53—55°C[12]).

The nitrosation of 3-chloropropiophenone was carried out in a manner similar to that in the case of 1-chloro-3-butanone.[3] Colorless prisms with a m. p. of 111—112°C was obtained in a 83% yield (lit. 113—114°C[12]; 110—110.5°C[2]).

The Reaction of 3-Chloro-2-oximinopropiophenone with Barium Thiocyanate.—A solution of barium thiocyanate (3 g.) in ethanol (15 ml.) was gradually added to a solution of 3-chloro-2-oximinopropiophenone (4 g.) in ethanol (20 ml.), and then the mixture was refluxed for 1 hr. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to give an brown residue, which was treated with activated charcoal in benzene (20 ml.). After the benzene had been evaporated under reduced pressure, the residual red oil (4.5 g.) was allowed to stand at room temperature to crystallize. The crystalline product was purified by passing the methanolic solution through an alumina column. Recrystallization from benzene gave 2-oximino-3-oxo-3-phenylpropyl thiocyanate (XIV, R=C_6H_5) as colorless needles; m. p. 91—93°C. The product showed no color reaction with ferric chloride. IR: ν_{max}^{KBr} 2150 (–SCN) and 1670 cm^{-1} (–C=O).

Found: N, 12.79. Calcd. for $C_{10}H_8N_2O_2S$: N, 12.72%.

5-Phenyl-2-aminothiazole-1-oxide (XVIII). — A solution of barium thiocyanate (1.5 g.) in ethanol (15 ml.) was added, drop by drop, to a solution of *anti*-2-bromoacetophenone oxime[13] (XVI, 2 g.) in ethanol (20 ml.), and the mixture was warmed at 35°C for 1 hr. After the precipitated barium chloride was filtered off, the solution was concentrated under reduced pressure to give an oily product. The oily product was purified by means of unactivated-alumina column chromatography to yield a caramel (1.5 g.), which showed a blue color with ferric chloride and which had no infrared absorption in the region of the –SCN group. The picrate of XVIII was obtained by refluxing a solution of the caramel (0.5 g.) and picric acid (0.5 g.) in ethanol (40 ml.) for 1 hr., followed by the evaporation of the ethanol. Recrystallization from ethanol gave yellow plates; m. p. 171—172°C.

Found: C, 43.01; H, 2.82; N, 16.67. Calcd. for $C_{15}H_{11}N_5O_8S$: C, 42.76; H, 2.63; N, 16.63%.

12) T. Matsumoto and K. Hata, ibid., **79**, 5506 (1957).

13) H. Korton and R. Scholl, *Ber.*, **34**, 1907 (1901).