the expectation that this heterocyclic system would have spectral characteristics similar to those found in weakly aromatic systems such as furan. In this case, the empty *p*-orbital of the boron atom must be responsible for completion of the π-orbital network and thus 1,3,2-dioxaborole may be thought of as a heterolog of the tropylium cation.

EXPERIMENTAL[11]

2,4,5-Triphenyl-1,3,2-dioxaborole (I). This compound was prepared according to the directions of Letsinger and Hamilton.[5] The ultraviolet spectrum of I in cyclohexane was found to differ slightly from that reported by these authors.[5] I exhibited four maxima and a shoulder (——): (ϵ_{219} 29,000); ϵ_{222} 29,600; ϵ_{241} 13,500; ϵ_{283} 16,800; ϵ_{295} 16,800. In ethanol solution, I had but two maxima: ϵ_{221} 25,000; ϵ_{259} 12,700.

2-Isopropyl-4,5-diphenyl-1,3,2-dioxaborole (II). A benzene solution (250 ml.) containing 10 g. (0.11 mole) of 2-propaneboronic[12] acid and 24 g. (0.11 mole) of benzoin was heated for 20 hr. in a flask fitted with a take-off adapter to remove the water azeotrope. The benzene was removed at reduced pressure and the residue distilled (b.p. 140°/0.3 mm.) and then fractionated through a 2-ft. spinning band column to give 12 g. (40%) of a colorless liquid (b.p. 118°/0.2 mm.) which crystallized on standing, m.p. 46–47°. The ultraviolet spectrum in cyclohexane exhibited two maxima and two shoulders (——): ϵ_{222} 18,800; (ϵ_{239} 11,700); (ϵ_{257} 5850); ϵ_{299} 11,700. The spectrum in ethanol solution showed only two maxima: ϵ_{224} 11,900; ϵ_{258} 16,700.

Anal. Calcd. for $C_{17}H_{17}BO_2$: C, 77.28; H, 6.49. Found: C, 77.18; H, 6.70.

2-Phenyl-4,5-dimethyl-1,3,2-dioxaborole (III). Benzeneboronic acid (8 g., 0.07 mole) was allowed to react with practical grade 3-hydroxy-2-butanone (13 g., 0.15 mole) in 150 ml. of benzene as described above. Since the product was thermally sensitive, the crude material was distilled at 60–65°/0.7 mm. and then fractionated at 2 mm. (b.p. 79°). Although the product (6.6 g., 58%) crystallized on standing, analytical purity was not obtained until the compound was sublimed (40°/0.1 mm.); m.p. 46–47°.

The ultraviolet spectrum of III in cyclohexane contained four maxima and three shoulders (——): ϵ_{214} 7000; ϵ_{222} 5560; ϵ_{227} 5110; ϵ_{251} 6370; (ϵ_{260} 5830); (ϵ_{270} 4500); (ϵ_{277} 3050). In ethanol the spectrum exhibited two maxima and two shoulders (——): ϵ_{216} 9340; ϵ_{265} 1530; (ϵ_{273} 1430); (ϵ_{280} 1080).

Anal. Calcd. for $C_{10}H_{11}BO_2$: C, 69.02; H, 6.37. Found: C, 68.85; H, 6.32.

2-Isopropyl-4,5-dimethyl-1,3,2-dioxaborole (IV). 2-Propaneboronic[12] acid (28 g., 0.32 mole) was allowed to react with practical grade 3-hydroxy-2-butanone (28 g., 0.32 mole) in 300 ml. of benzene as described above. The benzene was removed at reduced pressure and the product distilled (b.p. 40–45°/15 mm.). Fractionation through a 2-ft. spinning band column yielded 9.1 g. (21%) of IV (b.p. 79–81.5°/90 mm).

The analytical sample had a b.p. of 81.5°/90 mm. and its ultraviolet spectrum in cyclohexane had one maximum, ϵ_{303} 2.4.

Anal. Calcd. for $C_7H_{13}BO_2$: C, 60.05; H, 9.36. Found: C, 60.26; H, 9.33.

Oxidation of IV. Approximately 250 mg. of IV was placed on a watch glass and allowed to stand exposed to the atmosphere. Within a few minutes, a white solid began to form around the edge of the liquid and the odor of biacetyl became very much apparent. The infrared spectrum (neat) of the oxidation product suggests the presence of 2-propaneboronic acid, biacetyl (1720 cm.$^{-1}$) and acetic anhydride (1760, 1825 cm.$^{-1}$).

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(10) Unfortunately the ultraviolet spectra of the monophenyl substituted furans have not been reported; however, those of the 2- and 3-*p*-chlorophenylfurans are recorded. Since the absorption of chlorobenzene (257 mμ, ϵ = 170)[9] is not significantly different from that of benzene (250 mμ, ϵ = 250),[9] it appears safe to assume that the spectra of the chlorophenylfurans are probably not markedly different from those of the phenylfurans. 2-*p*-Chlorophenyl- and 3-*p*-chlorophenylfuran have ϵ = 20,600 (287 mμ) and ϵ = 13,200 (262 mμ), respectively [A. W. Johnson, *J. Chem. Soc.*, 895 (1946)]. Here again we see the marked effect on the absorption intensity due to conjugation of a weakly absorbing system with a benzene ring.

(11) All melting points are corrected; boiling points are uncorrected. The ultraviolet spectra were determined with a Beckman DK-2 recording spectrophotometer.

(12) P. A. McCusker, E. C. Ashby, and H. S. Makowski, *J. Am. Chem. Soc.*, **79**, 5179 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

Synthesis of Aminoisoxazolones from α-Cyano Esters and Hydroxylamine[1]

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The reaction of α-cyano esters with hydroxylamine afforded either 3-amino-5- or 5-amino-3-isoxazolones or α-amidoxime hydroxamic acids, depending on the reaction conditions. These products were characterized by their acetamido, benzamido, and arenesulfonamido derivatives.

The reaction of hydroxylamine with ethyl cyanoacetate has been reported by Modeen[2] to afford the amidoxime hydroxamic acid, HONHCO—CH_2—C(=NH)NHOH. Further examination revealed this reaction to be more complex and a study of it was initiated using a number of α-cyano esters, I, ethyl cyanoacetate (R=H), ethyl α-cyano-β-methylvalerate (R=*sec*-butyl), ethyl α-cyano-α-cyclohexylacetate (R=cyclohexyl) and α-cyano-β-phenylpropionate (R = benzyl). From the reaction of each α-cyano ester with one mole of hydroxylamine in ethanol there were isolated two isomeric solids depending on the presence or absence of a

(1) This work was presented before the Division of Organic Chemistry at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 27, 1961.

(2) H. Modeen, *Ber.*, **27**, (Referate) 261 (1894).

sodium ethoxide catalyst. To elucidate the structure of the two isomers obtained from each cyano ester, it was imperative to study this reaction extensively, and for this purpose ethyl α-cyano-β-phenylpropionate, $C_6H_5CH_2CH(CN)CO_2C_2H_5$ (I; R = benzyl) was chosen as the typical α-cyano ester.

From the reaction of this ester with hydroxylamine, under various conditions, three crystalline products were isolated. They consisted of two isomers of molecular formula $C_{10}H_{10}N_2O_2$ and a third solid $C_{10}H_{13}N_3O_3$ which corresponded to Modeen's amidoxime hydroxamic acid. The preparation and proof of structure of the two isomers are described below.

When ethyl α-cyano-β-phenylpropionate was subjected to the conventional hydroxamic acid synthesis, with one mole of hydroxylamine and one mole of sodium ethoxide in ethanol at 25°, there was obtained (after acidification) isomer A, $C_{10}H_{10}N_2O_2$, m.p 147°. The same reaction with two moles of hydroxylamine afforded A in better yield accompanied by a small yield of isomer B, $C_{10}H_{10}N_2O_2$, m.p. 133°. The separation of the two isomers was possible by acidifying an aqueous solution of the product of the reaction, first with carbon dioxide, which precipitated A, and then with dilute hydrochloric acid which gave B. However, it was found that only isomer B was formed when the ester was treated with hydroxylamine in hot ethanol without sodium ethoxide. In the residual fractions of this experiment, isomer A could not be detected (infrared spectra).

From their chemical behavior and spectra, it became evident that A and B did not possess the expected isomeric α-cyano hydroxamic acid structures, $C_6H_5CH_2CH(CN)CO$–NHOH or $C_6H_5CH_2$-CH(CN)CO—ONH_2. With aqueous ferric chloride solution, hydroxamic acids of type RCONHOH invariably exhibit a characteristic deep purple color, but with A this reagent turned reddish brown and with B remained yellow. Benzoylation of hydroxamic acid affords *O*-benzoyl hydroxamic acids, RCO-NH—$OCOC_6H_5$ which are acids and are soluble in dilute cold aqueous sodium hydroxide solution, but the benzoyl derivatives of A and B were quite insoluble in that medium. It has also been shown that hydroxamic acids, RCONHOH, rearrange spontaneously with sulfonyl halides in a basic medium,[3] and only hydroxamic acids devoid of the hydrogen atom on nitrogen *e.g.*, *N*-hydroxy imides, $(RCO)_2$-N—OH, form stable sulfonyl esters.[4] Treatment of A and B with arenesulfonyl halides readily yielded sulfonyl derivatives. Absorption in the infrared spectra of A and B in the 1500–1800 cm.$^{-1}$ region was considerably more complex than expected for the α-cyano hydroxamic structure; the assignment of bands will be discussed fully in the following paper.[5]

On the basis of these observations, alternate structures for A and B were sought. It seemed quite reasonable to assume that the intermediate α-cyano hydroxamic acid had cyclized to an isoxazole derivative. Inasmuch we had to account for two isomers, it became evident that elucidation of their structures depended on their unequivocal syntheses. This was possible for isomer A.

Condensation of ethyl α-cyano-β-phenylpropionate with benzyloxyamine in the presence of sodium ethoxide afforded, albeit in small yield, *O*-benzyl α-cyano-β-phenylpropionohydroxamic acid $C_6H_5CH_2CH(CN)$—$CONHOCH_2C_6H_5$, accompanied by α-cyano-β-phenylpropionic acid. The structure[6] of this *O*-benzyl hydroxamic acid was proved by elemental analysis, its solubility in 10% sodium hydroxide solution and its infrared spectrum in chloroform, which revealed a single strong absorption band at 1700 cm.$^{-1}$ Furthermore, the cyano group was detected as a weak sharp band at 2228 cm.$^{-1}$ A similar band at 2250 cm.$^{-1}$ was found for the cyano group in ethyl α-cyano-β-phenylpropionate (pure liquid). Reduction of *O*-benzyl α-cyano-β-phenylpropionohydroxamic acid over palladium on charcoal[7] cleaved off the benzyl group, and there was isolated isomer A which was further characterized by its benzoyl derivative. The solution obtained immediately after the reduction was colored red rather than purple when tested with ferric chloride. This would indicate that if the α-cyano hydroxamic acid is an intermediate, it cyclizes immediately to isomer A (R is benzyl).

From these observations, the mode of formation of A and B are postulated and are summarized in Chart 1. In the base catalyzed reaction, nucleophilic attack by hydroxylamine occurs first at the carbonyl carbon of the ester group of I to form the hydroxamate ion derived from the α-cyano hydroxamic acid II. Nucleophilic attack of the hydroxamate ion on the neighboring electrophilic carbon of the cyano group then forms the isoxazole derivative A. This isomer may exist as a number of tautomeric structures[8,9] of which three have been presented on Chart 1, *viz.*, as a 5-imino-3-isoxazolidone

(3) (a) C. D. Hurd and L. Bauer, *J. Am. Chem. Soc.*, **76**, 2791 (1954); (b) M. A. Stolberg *et al.*, *J. Am. Chem. Soc.*, **77**, 765 (1955).

(4) (a) L. Bauer and S. V. Miarka, *J. Org. Chem.*, **24**, 1293 (1959); (b) E. Kühle and R. Wegler, *Ann.*, **616**, 183 (1958).

(5) C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **26**, 4923 (1961).

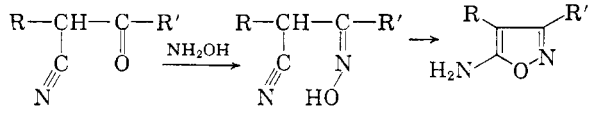
(6) J. H. Cooley, W. D. Bills, and J. R. Throckmorton, *J. Org. Chem.*, **25**, 1734 (1960) have reported the carbonyl band for *O*-alkyl hydroxamic acids. For example CH_3CO-$NHOCH_2C_6H_5$ (pure liquid) absorbs at 1670 cm.$^{-1}$; furthermore these *O*-alkyl hydroxamic acids are soluble in 20% sodium hydroxide solution.

(7) D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631, 3518 (1955) and 2310 (1959) have shown that *O*-benzyl hydroxamates are readily reduced to the parent hydroxamic acid.

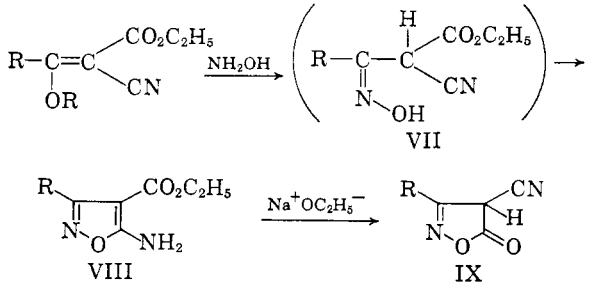
(8) For a discussion of this type of tautomerism see, R. A. Barnes in "Isoxazoles," Vol. V of R. C. Elderfield's "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 472.

(IIIa), a 5-amino-3-isoxazolone (IIIb), or as the 5-amino-3-isoxazolol (IIIc). We prefer the 5-amino-3-isoxazolone structure (IIIb), or rather a resonance hybrid of it,[5] for all of the members of the isomer A series. In the reaction of I with hydroxylamine in hot ethanol in the absence of sodium ethoxide, we have assumed that hydroxylamine adds preferentially to the nitrile group to afford the amidoxime ester (IV), which then spontaneously cyclizes to the isoxazole derivative, represented by the tautomers Va, Vb, and Vc. Again, we prefer the 3-amino-5-isoxazolone structure (Vb) for compounds belonging to the isomer B series.[5]

In general, the synthesis of 5-aminoisoxazoles is based on the reaction of hydroxylamine with β-oxo nitriles, presumably through the cyclization of the intermediate β-oximino nitriles.[10] In the same



vein, it is interesting to compare our syntheses with the recent reports on the reaction of hydroxylamine with α-cyano-β-alkoxyacrylates[11,12] to form 4-carbethoxy-5-aminoisoxazoles (VIII), presumably *via* the intermediate α-cyano-β-oximino ester (VII). It was also reported[11] that isomerization of VIII to 4-cyano-5-isoxazolone (IX) occurred with sodium ethoxide in ethanol solution, presumably *via* VII. In these reactions also, cyclization of the oxime VII in the neutral medium took place preferentially on the nitrile group but in the presence of sodium ethoxide (VII) cyclized, presumably *via* the oxime anion of VII, on the ester group.



The various members of the two series A and B, each reacted readily with boiling acetic anhydride and benzoyl chloride either in pyridine or under Schotten-Baumann conditions to afford derivatives which we have formulated as amides. Similar reaction with arenesulfonyl chlorides in pyridine yielded highly crystalline solids which analyzed as the corresponding sulfonamides. Their infrared spectra and structure will be discussed fully in the following paper.[5]

The reaction of I with three moles of hydroxylamine in hot ethanol yielded the α-amidoxime hydroxamic acids VI, whose structures were established by elemental analysis and infrared spectra. They are colorless solids which gave a purple color with ferric chloride and were characterized by their benzoyl derivatives, C_6H_5CO—ONHCOCH(R)C(=NH)NHO—COC_6H_5. One of these α-amidoxime hydroxamic acids (VI; R = benzyl) could be converted to isomer B, Vb (R = benzyl).

EXPERIMENTAL[13]

Method A. 5-Amino-3-isoxazolones (IIIb). The α-cyano ester (I; 0.05 mole) was dissolved in an ice-cold ethanolic solution of hydroxylamine [from 3.85 g. (0.055 mole) of hydroxylamine hydrochloride in 100 ml. of ethanol and an equivalent amount of sodium ethoxide], and an ethanolic sodium ethoxide solution [from 1.15 g. (0.05 g.-atom) of sodium in 30 ml. of ethanol] was added. The reaction mixture was allowed to stand at 25° for 15–18 hr. Ethanol was removed *in vacuo* at 35°. The gummy residue was washed with dry ether (50 ml.) and then petroleum ether (b.p. 30–60°) and the residue was dried *in vacuo*. The product was dissolved in ice water (30–50 ml.), and carbon dioxide bubbled through this ice-cold solution for 1.5 to 3 hr. The product was filtered, washed with a little ice-cold water, and dried and crystallized (*vide* Table I).

In the preparation of 5-amino-3-isoxazolone (IIIb; R = H), the aqueous solution of the sodium salt was neutralized with ice-cold 1:3 hydrochloric acid to *p*H 7 when the product crystallized.

Method B. 3-Amino-5-isoxazolones (Vb). The α-cyano ester (I; 0.05 mole) was added to an ethanolic solution of hydroxylamine [from 3.85 g. (0.055 mole) of hydroxylamine hydrochloride and an equivalent amount of sodium ethoxide]. The reaction mixture was kept at 50–60° for 1 hr. and then refluxed for 2 hr. and left overnight at 25° (15–18 hr.). Ethanol was evaporated *in vacuo* and the gummy residue dissolved in minimum amount of warm *n*-butyl alcohol (5–10 ml.). The addition of ligroin (b.p. 30–60°) afforded the solid on standing (*vide* Table II).

The reaction of ethyl α-cyano-α-cyclohexylacetate afforded crystals immediately on trituration of the gummy residue with warm *n*-butyl alcohol.

Ethyl cyanoacetate did not yield 3-amino-5-isoxazolone (Vb; R = H) under these general conditions. Instead a red gum was isolated which consisted mainly of the amidoxime hydroxamic acid, VI (R = H).

Method C. Acetamido derivatives. The isoxazolone (0.005 mole) was suspended in 12 ml. of acetic anhydride and boiled for 2 min. The resulting solution was cooled, diluted with 24 ml. of water and the solvents removed *in vacuo*. The crude product yielded the pure acetamido isoxazolones on a single crystallization (*vide* Tables I and II).

The reaction of acetic anhydride with 5-amino-3-isoxazolong (IIIc; R = H) afforded crystals, m.p. 178–179° (from ethyl acetate–benzene) which did not have the correct analysis for the expected acetyl derivative.

Method D. Benzamido derivatives by the Schotten-Baumann method. The isoxazolone (0.0075 mole) was dissolved in cold

(9) For a recent discussion on the 5-hydroxyisoxazole-5-isoxazolone tautomerism and one on 3- and 5-aminoisoxazoles see A. J. Boulton and A. R. Katritsky, *Tetrahedron*, **12**, 41, 51 (1961).

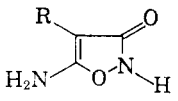
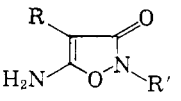
(10) W. Logemann, L. Almirante, and L. Caprio, *Chem. Ber.*, **87**, 1175 (1954); L. Almirante, A. Bianchi, and V. Zamboni, *Ann. di Chim., Rome*, **46**, 623 (1956); *Chem. Abstr.*, **54**, 9629 (1957).

(11) A. Dornow and H. Teckenburg, *Chem. Ber.*, **93**, 1104 (1960).

(12) H. Kano, Y. Makisumi, and K. Ogata, *Chem. Pharm. Bull., Japan*, **6**, 105 (1958).

(13) Melting points are uncorrected. Analyses are by Dr. Kurt Eder, Geneva, Switzerland.

TABLE I

ISOMERS A: 5-AMINO-3-ISOXAZOLONES,  AND DERIVATIVES, 

R	R′	Method of Prep.	Solvent of Cryst.	Yield, %	M.P. (Dec.)	Molecular Formula		C, %	H, %	N, %
H		A	Ethanol-ligroin (b.p. 30–60)	44	152–153	$C_3H_4N_2O_2$	Calcd.	36.00	4.02	27.99
							Found	36.17	4.14	27.91
sec-C_4H_9		A	Ethyl acetate	62	151–153	$C_7H_{12}N_2O_2$	Calcd.	53.83	7.74	17.94
							Found	53.81	7.60	17.91
Cyclo-C_6H_{11}		A	Benzene	68	133–137	$C_9H_{14}N_2O_2$	Calcd.	59.34	7.69	15.38
							Found	59.51	7.76	15.36
$C_6H_5CH_2$		A	Ethyl acetate	68	147	$C_{10}H_{10}N_2O_2$	Calcd.	63.16	5.26	14.73
							Found	63.37	5.40	14.76
sec-C_4H_9	CH_3CO	C	Benzene	56	183–184	$C_9H_{14}N_2O_3$	Calcd.	54.53	7.12	14.14
							Found	54.59	6.95	14.20
Cyclo-C_6H_{11}	CH_3CO	C	Benzene	99	131–132	$C_{11}H_{16}N_2O_3$	Calcd.	58.91	7.19	12.49
							Found	59.14	7.09	12.41
$C_6H_5CH_2$	CH_3CO	C	Ethyl acetate–hexane	87	151	$C_{12}H_{12}N_2O_3$	Calcd.	62.06	5.21	12.13
							Found	61.94	5.44	12.05
H	C_6H_5CO	D	Ethyl acetate	10	177–179	$C_{10}H_8N_2O_3$	Calcd.	58.82	3.95	13.72
							Found	58.96	4.02	13.83
sec-C_4H_9	C_6H_5CO	E	Benzene	38	133–135	$C_{14}H_{16}N_2O_3$	Calcd.	64.60	6.19	10.76
							Found	64.62	6.22	10.51
Cyclo-C_6H_{11}	C_6H_5CO	D	Ethyl acetate	30	189–190	$C_{16}H_{18}N_2O_3$	Calcd.	67.13	6.29	9.79
							Found	67.17	6.42	9.89
$C_6H_5CH_2$	C_6H_5CO	D	Ethyl acetate	60	168	$C_{17}H_{14}N_2O_3$	Calcd.	69.39	4.80	9.53
							Found	69.75	4.78	9.75
H	$C_6H_5SO_2$	E	Ethyl acetate	58	171–172	$C_9H_8N_2O_4S$	Calcd.	45.00	3.33	11.66
							Found	45.12	3.43	11.64
sec-C_4H_9	*p*-$CH_3C_6H_4SO_2$	E	Benzene	50	153–154	$C_{14}H_{18}N_2O_4S$	Calcd.	54.18	5.81	9.03
							Found	54.13	5.93	9.19
Cyclo-C_6H_{11}	$C_6H_5SO_2$	E	Ethyl acetate–benzene	50	164–165	$C_{15}H_{18}N_2O_4S$	Calcd.	55.90	5.59	8.69
							Found	56.01	5.74	8.75
$C_6H_5CH_2$	*p*-$CH_3C_6H_4SO_2$	E	Ethyl acetate–benzene	90	172	$C_{17}H_{16}N_2O_4S$	Calcd.	59.28	4.68	8.14
							Found	59.20	4.76	8.19

sodium hydroxide (0.4 g. in 10 ml. of water) and stirred with benzoyl chloride (1.2 ml.) for 1 hr. The solid product was collected and washed with water. Purification was effected by crystallization from benzene or ethyl acetate (*vide* Tables I and II for derivatives.)

Method E. Benzamido derivatives by pyridine method. The isoxazolone (0.005 mole) was dissolved in pyridine (8 ml.). Benzoyl chloride (1.0 ml.) was added and the mixture warmed on the steam bath for 15–45 min. The solution was then poured into ice-cold 1:5 hydrochloric acid (50 ml.). Usually an oil was obtained which solidified on standing. The crude product yielded the pure derivative after two or three recrystallizations. (*vide* Tables I and II).

Method F. Arenesulfonamido derivatives. The isoxazolone (0.005 mole) was dissolved in 8 ml. of pyridine and was gradually mixed with the arenesulfonyl chloride (0.005 mole; either benzene- or *p*-toluenesulfonyl chloride), and the reaction mixture was then warmed on a steam bath for 1 hr. The reaction mixture was then poured into ice-cold 1:5 hydrochloric acid (50 ml.). An oil usually separated which solidified on standing after 1–2 hr. The solid product was triturated with petroleum ether (b.p. 30–60°) and the pure derivative was obtained after several recrystallizations (*vide* Tables I and II).

Method G. α-Amidoxime hydroxamic acids (VI). Finely powdered hydroxylamine hydrochloride (11.55 g.; 0.165 mole) was suspended in absolute ethanol (75 ml.) in a three necked flask equipped with a mechanical stirrer and a condenser. A little phenolphthalein was also added. Sodium hydride (3.96 g.; 0.165 mole) was gradually added during the course of 0.5 hr. so that the color of phenolphthalein never predominated. The mixture was stirred for another 0.5 hr. The sodium chloride was filtered and the α-cyano ester (0.05 mole) was added to the filtered ethanolic hydroxylamine solution. The reaction mixture was kept at 50–60° for 1 hr. and then refluxed for two hr., and allowed to stand at 25° overnight. Solvents were evaporated off *in vacuo* and the resulting gum was dissolved in a minimum amount of warm *n*-butyl alcohol (5–10 ml.). On dilution with benzene the amidoxime hydroxamic acid crystallized after some time (*vide* Table III).

In the reaction of ethyl α-cyano- β-methylvalerate (I; R = *sec*-butyl), the amidoxime hydroxamic acid refused to solidify and the gum converted to the dibenzoyl derivative (see below, method H).

In the preparation of VI, R = cyclohexyl, the gum crystallized when *n*-butyl alcohol alone was added to the gummy residue.

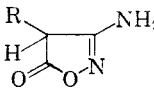
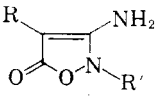
The derivative VI, R = H, crystallized from the original reaction mixture.

All of these α-amidoxime hydroxamic acids decomposed appreciably during recrystallizations. The yields quoted in Table III are those obtained from the reaction mixture.

Conversion of VI *to an isomer B (R = benzyl).* A solution of VI (R = benzyl; 1.0 g.) in water (7.0 ml.) was boiled for 1 min. A clear yellow solution was obtained. Dilute (1:3) hydrochloric acid (2 ml.) was added and crystals of Vb (0.4 g. or 46.5%) were formed after this solution had stood overnight.

Method H. Benzoyl derivatives of α-amidoxime hydroxamic acids. The amidoxime hydroxamic acid (0.01 mole) was dissolved in pyridine (15 ml.) and the solution cooled in ice. Benzoyl chloride (3.0 ml.) was gradually added with stirring and the reaction mixture stirred at 25° for 2 hr. Then it

TABLE II

ISOMERS B: 3-AMINO-5-ISOXAZOLONES,  AND DERIVATIVES, 

R	R′	Method of Prep.	Solvent of Cryst.	Yield, %	M.P. (Dec.)	Molecular Formula		C, %	H, %	N, %
sec-C_4H_9		B	Benzene	13	121–122	$C_7H_{12}N_2O_2$	Calcd.	53.83	7.74	17.94
							Found	53.76	7.58	18.02
Cyclo-C_6H_{11}		B	Ethyl acetate	17	190–191	$C_9H_{14}N_2O_2$	Calcd.	59.34	7.69	15.38
							Found	59.45	7.71	15.49
$C_6H_5CH_2$		B	Ethyl acetate–benzene	38	133	$C_{10}H_{10}N_2O_2$	Calcd.	63.16	5.26	14.73
							Found	63.54	5.28	14.73
sec-C_4H_9	CH_3CO	C	Cyclohexane	81	107–108	$C_9H_{14}N_2O_3$	Calcd.	54.53	7.12	14.14
							Found	54.61	7.02	14.17
Cyclo-C_6H_{11}	CH_3CO	C	Benzene	80	192–193	$C_{11}H_{16}N_2O_3$	Calcd.	58.91	7.19	12.49
							Found	59.04	7.11	12.60
$C_6H_5CH_2$	CH_3CO	C	Benzene-hexane	—	144–145	$C_{12}H_{12}N_2O_3$	Calcd.	62.06	5.21	12.13
							Found	62.33	5.14	12.16
sec-C_4H_9	C_6H_5CO	E	Cyclohexane	43	92	$C_{14}H_{16}N_2O_3$	Calcd.	64.60	6.19	10.79
							Found	64.75	6.04	10.86
Cyclo-C_6H_{11}	C_6H_5CO	E	Benzene	89	161–162	$C_{16}H_{18}N_2O_3$	Calcd.	67.13	6.29	9.73
							Found	66.92	6.30	9.78
$C_6H_5CH_2$	C_6H_5CO	D	Ethyl acetate	63	171–172	$C_{17}H_{14}N_2O_3$	Calcd.	69.39	4.80	9.53
							Found	69.52	4.73	9.88
sec-C_4H_9	*p*-$CH_3C_6H_4SO_2$	F	Benzene	71	122–123	$C_{14}H_{18}N_2O_4S$	Calcd.	54.18	5.81	9.03
							Found	54.40	5.74	8.99
Cyclo-C_6H_{11}	*p*-$CH_3C_6H_4SO_2$	F	Benzene	99	162–163	$C_{16}H_{26}N_2O_4S$	Calcd.	57.13	5.99	8.38
							Found	57.19	6.00	8.45
$C_6H_5CH_2$	*p*-$CH_3C_6H_4SO_2$	F	Ethyl acetate	88	202–203	$C_{17}H_{16}N_2O_4S$	Calcd.	59.28	4.68	—
							Found	59.00	4.60	—

TABLE III

α-AMIDOXIME HYDROXAMIC ACIDS AND THEIR BENZOYL DERIVATIVES, R—CH(CONHOR′)(C(=NH)NHOR′)

R	R′	Method of Prep.	Solvent of Cryst.	Yield, %	M.P.	Molecular Formula		C, %	H, %	N, %
H	H	G	50% Aqueous ethanol	94	152–153[a]	$C_3H_7N_3O_3$	Calcd.	27.07	5.30	31.57
							Found	27.16	5.33	31.54
Cyclo-C_6H_{11}	H	G	Dioxane	74	167–170	$C_9H_{17}N_3O_3$	Calcd.	50.22	7.96	—
							Found	50.24	8.23	—
$C_6H_5CH_2$	H	G	2-Propanol–benzene	56	133	$C_{10}H_{13}N_3O_3$	Calcd.	53.81	5.86	18.82
							Found	53.86	5.44	18.29
H	C_6H_5CO	H	2-Propanol	80	165–166[b]	$C_{17}H_{15}N_3O_5$	Calcd.	59.82	4.43	12.31
							Found	59.98	4.36	12.39
sec-C_4H_9	C_6H_5CO	H	Ethyl acetate	61	170–171	$C_{21}H_{23}N_3O_5$	Calcd.	63.46	5.83	10.57
							Found	63.64	5.76	10.79
Cyclo-C_6H_{11}	C_6H_5CO	H	Methanol	73	182–183	$C_{23}H_{25}N_3O_5$	Calcd.	65.23	5.95	9.92
							Found	65.24	6.10	10.04
$C_6H_5CH_2$	C_6H_5CO	H	Benzene–ethyl acetate	47	160	$C_{24}H_{21}N_3O_5$	Calcd.	66.81	4.91	9.74
							Found	66.79	4.91	9.84

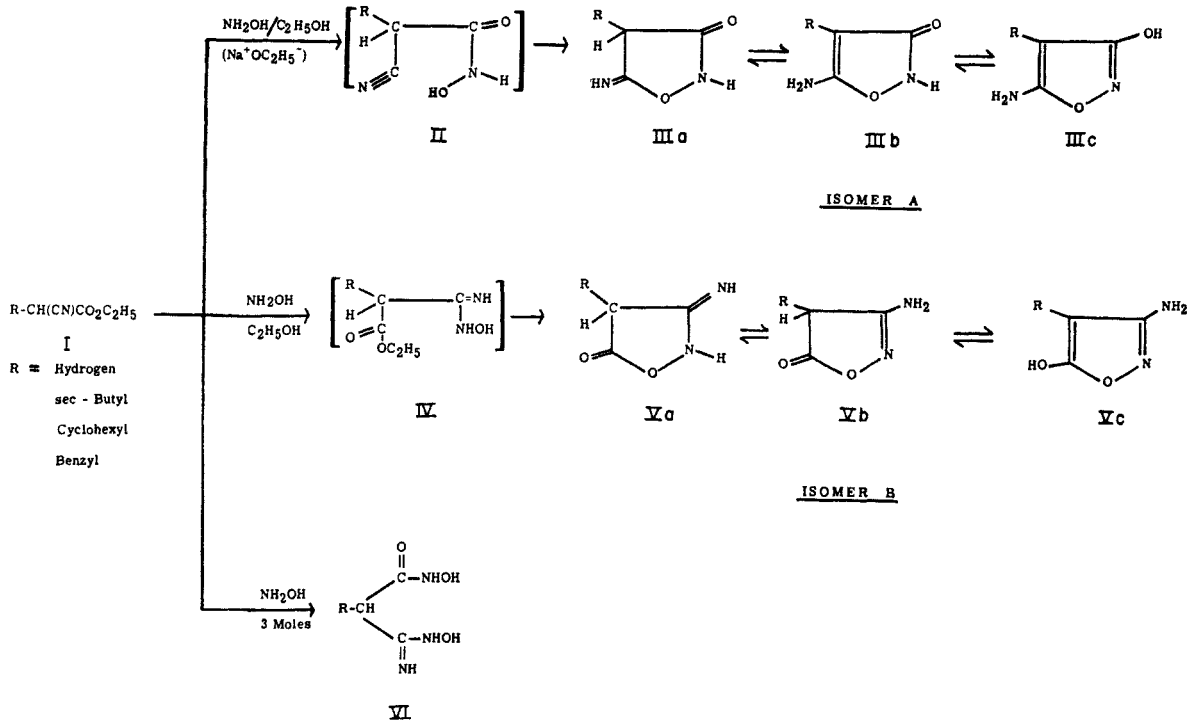
[a] Lit.[2] m.p. 150–152°. [b] Lit.[2] m.p. 165°.

was poured into 100 ml. of water. The separated oil readily crystalized (*vide* Table III).

Unequivocal synthesis of 4-benzyl-5-amino-3-isoxazolone, IIIb (*R* = *benzyl*). *O-Benzyl α-cyano-β-phenylpropionohydroxamic acid.* A mixture of ethyl α-cyano-β-phenylpropionate (6.8 g.; 0.033 mole) and benzyloxyamine[14] (4.1 g.; 0.033 mole) in sodium ethoxide solution (0.766 g. of sodium in 20 ml. of ethanol) was allowed to stand at 25° for 4 days. Ethanol was removed *in vacuo* and the residue dissolved in water (25 ml.) acidified with cold concentrated hydrochloric acid. The aqueous layer was extracted with ether (20 ml.) and chloroform (50 ml.). The organic layers were first washed with 5% sodium bicarbonate solution, then with 10% sodium hydroxide solution. Acidification of the sodium hydroxide extract afforded the hydroxamic acid (1.4 g.;

(14) Made by F. M. Hershenson and R. Mrtek using Method C described by A. F. MacKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38**, 343 (1960).

CHART I



15%), m.p. 105–110°. Recrystallization from benzene yielded needles (1.0 g.; 10.7%), m.p. 115°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.3): C, 72.81; H, 5.75; N, 9.99. Found: C, 72.99; H, 5.65; N, 10.07.

After acidifying of the sodium bicarbonate extract and ether extraction, there was collected α-cyano-β-phenylpropionic acid (1.6 g.; 28%), m.p. 100–101° (from benzene).

The *O*-benzyl hydroxamic acid (0.7 g.; 0.0025 mole) was reduced with hydrogen at 30-lb. pressure at 25° in ethanol (35 ml.) over 5% palladium on charcoal (0.05 g.). After 1.5 hr., ethanol was distilled *in vacuo* and the oily residue boiled to dryness twice with benzene to remove the last traces of ethanol when a crystalline solid was obtained. The crude solid (0.22 g.; 48.4%) melted at 128–129°. One crystallization from benzene containing some ethyl acetate afforded a solid which was identical in all respects to isomer A, IIIb (R = benzyl). Benzoylation of this product afforded a benzoyl derivative, melting point and mixed melting point with the benzoyl derivative of isomer A, 168°, their infrared spectra were identical.

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