Reaction of 1,4,5,6-Tetrahydronicotinamide with Hydroxylamine[1]

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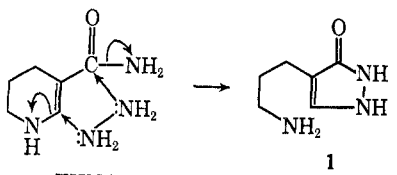
The ring of 1,4,5,6-tetrahydronicotinamide (THNA) is opened on reaction with an equivalent of hydroxylamine at room temperature, and a new heterocyclic compound, 4-(3-aminopropyl)-2-isoxazolin-5-one, is formed. This compound is also susceptible to ring opening and readily forms 5-amino-2-cyanopentanoic acid. The acid also is the major product when the THNA–hydroxylamine reaction is conducted at elevated temperatures. With a large excess of hydroxylamine, still another compound, 2-hydroximinopiperidine, can be formed from these reactants. The precursor of this compound is the 5-amino-2-cyanopentanoic acid formed from the isoxazolone. Any of the three products may be obtained in good yield.

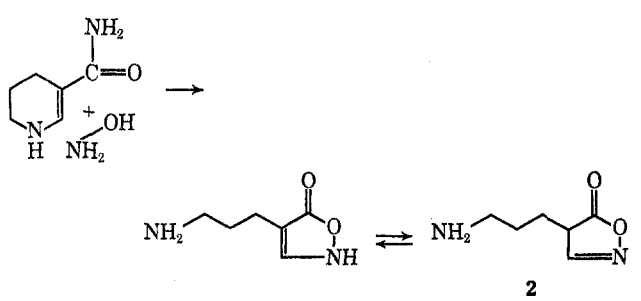
THNA was shown earlier[2] to be easily obtained by atmospheric pressure hydrogenation of nicotinamide over palladium. In exploring the properties of this new structure, it was found that hydrazine reacted at both the enamine and the amide sites, cleaving the original pyridine ring and forming 4-(3-aminopropyl)-2-pyrazolin-5-one (1) in high yield. It would appear that



THNA 1

other binucleophiles should react similarly with THNA or related 3-acyltetrahydropyridines, thereby forming various heterocycles with the aminopropyl substituent. In the present paper, results of a study of the reaction of hydroxylamine with THNA are given. It will be seen that the expected reaction occurs, and an isoxazolone (2) can be obtained. Depending on the reaction conditions, however, two other compounds could also result. Any of the three could be made the major product, and since all are novel structures, the reaction has proved to be of some synthetic value.

Isoxazolone Formation.—When the reaction of THNA with one equivalent of free hydroxylamine was conducted at room temperature in aqueous alcohol solution, the product was 4-(3-aminopropyl)-2-isoxazolin-5-one (2). The use of aqueous or ethanolic hydroxylamine hydrochloride caused formation of 2 at a



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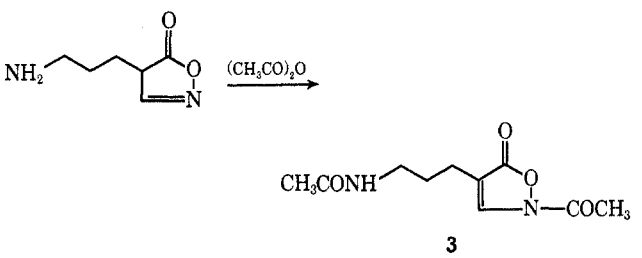
faster rate, suggesting the possibility of acid catalysis of the reaction. The mechanism of the reaction has not been studied; it is possible that the first step is addition of the nucleophile to the double bond, followed by ring-opening, rather than a direct displacement at the 2 position as implied in the equation above. The course of the reaction was easily followed by uv spectroscopy. THNA has a strong maximum at 285 mμ; this diminished as the reaction proceeded, while a maximum at 255 mμ for 2 developed. Reactions were stopped when the 285 mμ maximum had vanished. Ethyl tetrahydronicotinate also reacted with hydroxylamine (but not its hydrochloride) to form 2.

The isoxazolone proved difficult to isolate and purify; it was a hydroscopic solid easily undergoing ring-opening. While some spectroscopic measurements were made directly on 2, analysis was performed on the diacetyl derivative (3). Although the ring acetyl was particularly sensitive to hydrolysis, this derivative was suitable for characterization of 2.



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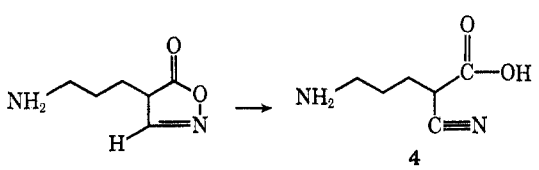
That hydroxylamine had attacked as indicated and not in the reverse sense (*i.e.*, $-NH_2$ attacking at carbonyl) is clear from the structure of the ring-opened product, 5-amino-2-cyanopentanoic acid (4). This reaction is described more fully in the next section.



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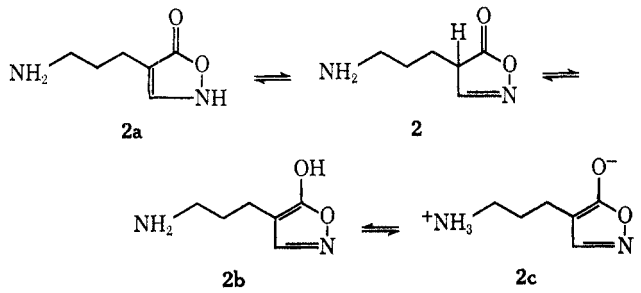
Isoxazolones may be involved in tautomeric changes; 2-unsubstituted 5-isoxazolones are generally expressed with the double bond in the 2 position. However, an added complication existed for 2, as revealed especially by its infrared spectrum (KBr). There was no signal for the carbonyl group, and strong broad absorption over the range 3600–2600 cm^{-1} suggested[3] the presence

(1) From the Ph.D. Dissertation of D. O. Pinion, Duke University, 1969. Presented at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968.

(2) P. M. Quan and L. D. Quin, *J. Org. Chem.*, **31**, 2487 (1966).

(3) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 96–97.

of $-NH_3^+$ rather than NH_2. Similar spectral features were found[2] for pyrazolone **1**. Insolubility in ether and other nonpolar solvents also indicated a dipolar structure. Structure **2c** is proposed for the solid isoxazolone, although in solution equilibria involving several forms may prevail.

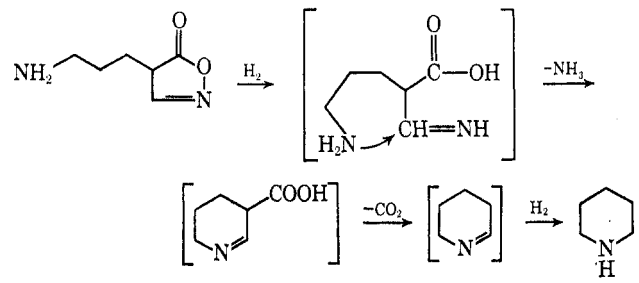


The mobility of the C-4 proton, as seen in **2** ⇄ **2b**, is a well known property of 2-isoxazolin-5-ones, which are acidic substances (*e.g.*, 4-methyl-2-isoxazolin-5-one, $pK_a = 4.5$[4]). Zwitterion formation would be a natural consequence of the presence of a group of this acidity with a primary amino group. The nmr spectrum (D_2O) reveals the absence of a proton at C-4; signals were obtained only for the three methylene groups and the C-3 proton. The latter was markedly deshielded (δ 8.0 ppm), as noted also for pyrazolone **1**.[2]

Amphoteric properties as required by formulation **2c** were demonstrated by paper electrophoresis studies. The primary amino group gave the usual color reaction with ninhydrin, making possible easy detection of migration. In acetic acid solution, the compound migrated toward the cathode. In a pH 10.6 buffer, movement occurred toward the anode. 5-Aminopentanoic acid, used for comparative purposes, had similar mobility in the two systems. It was established that the basic buffer did not cause ring-opening of the isoxazolone by eluting the compound from the paper prior to ninhydrin treatment. The uv maximum (258 mμ) was the same as that found for a solution of the isoxazolone in the same buffer; the ring-opened product **4** has a maximum near 210 mμ.

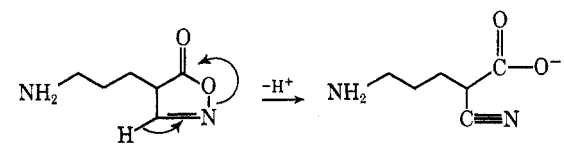
Spectral features of the diacetyl derivative (**3**) were also helpful in defining the structure of the parent isoxazolone. This derivative cannot participate in the tautomeric changes, and in addition to carbonyl stretching at 1641 (primary amide) and 1717 cm^{-1} (acetyl on ring[5]), there was a strong signal at 1749 cm^{-1} readily attributed to the ring carbonyl.[5] As noted, the isoxazolone showed no carbonyl band, consistent with form **2c**. N–H stretching in **3** was also quite different, and consisted of a sharp amide signal at 3294 cm^{-1}. The electron-withdrawing ring acetyl of **3** caused a downfield shift of the nmr signal for the C-3 proton to δ 8.40 ppm.

Hydrogenation at atmospheric pressure over Adams' catalyst opened the isozazolone ring. The only product isolated proved to be piperidine, whose formation can be accounted for by the series below (the exact sequence of the steps is not known).



5-Amino-2-cyanopentanoic Acid Formation.—When 1:1 or 2:1 mixtures of hydroxylamine and THNA were refluxed in methanol for 24 hr, an entirely different product resulted. It was established as **4** from (1) its amphoteric behavior, seen by paper electrophoresis and titrations, which with both acid and base gave values in accord with **4**, (2) the presence in its infrared spectrum of a C≡N stretching band (2247 cm^{-1}) and typical amino acid signals[3] ($-NH_3^+$ at 3100–2600 and 2123, $-COO^-$ at 1639 and 1376), and (3) facile acid hydrolysis, accompanied by decarboxylation, to a known compound, 5-aminopentanoic acid (**5**). Acid **4** had no uv maximum above 210 mμ. It readily lost carbon dioxide on melting.

Acid **4** originated from isoxazolone **2**, the initial product. An aqueous solution of the isoxazolone heated on the steam bath lost the characteristic uv maximum at 255 mμ after 3 hr. A 64% yield of **4** was then isolated. A similar yield of **4** resulted from refluxing the isoxazolone in ethanol for 2 hr. The ring-opening process can be accounted for in the following manner. At the time



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this reaction was observed in this laboratory, the ring-opening reaction of 3-unsubstituted isoxazolones[6] was novel. However, very recently[4] two 4-alkyl-2-isoxazolin-5-ones have been reported to undergo the same ring-opening process under mild conditions.

Acid **4** is a new compound and may be practically synthesized with the reaction described herein. For this, we prefer to preform the isoxazolone and then reflux it in ethanol, from which **4** precipitates. The overall yield from THNA is 67%.

2-(Hydroximino)piperidine Formation.—Refluxing an aqueous ethanol solution of THNA with a large excess (5:1) of hydroxylamine gave still another product, in moderate yield (32.2%) but good purity. A deposit of white solid developed in the condenser; it was identified as ammonium carbonate (and/or bicarbonate). A decarboxylation reaction was indicated, and indeed the formula of the compound ($C_5H_{10}N_2O$) required this. The compound was quite soluble in water, giving a basic solution. An attempt at acid hydrolysis was not successful when conducted in 6 *N* hydrochloric acid at 110° for 19 hr; only the hydrochloride of the base resulted. However, in 3 *N* acid for a longer period (3 days reflux), enough hydrolysis did occur to permit the detection of some 5-aminopentanoic acid (**5**) in the mixture.

(4) F. DeSarlo and G. Dini, *J. Heterocycl. Chem.*, **4**, 533 (1967).

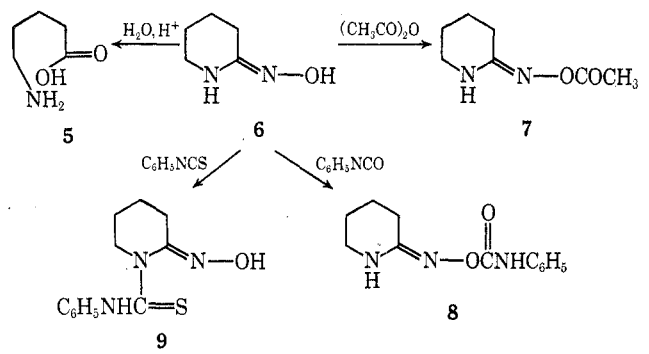
(5) C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **26**, 4923 (1961).

(6) Indeed, only one such compound (4-carboethoxy-2-isoxazolin-5-one) had been reported: L. Claisen, *Chem. Ber.*, **30**, 1481 (1897); S. Ruhemann, *ibid.*, **30**, 1083, 2031 (1897).

The infrared spectrum showed no bands for nitrile or carbonyl. A complex series of peaks (sharp but weak at 3413, broad and weak at 3096 and several broad bands over the range 2830–2400 cm^{-1}) suggested the presence of NH and OH groups, and the pattern resembled that of an amidoxime.[7] Pointing to the same possible structure was a sharp band at 1644 cm^{-1} suggesting C=N stretching. Confirming the amidoxime possibility, ferric chloride gave the magenta color characteristic of these compounds,[8] a precipitation test[9] with ferric nitrate–potassium isothiocyanate was positive, and a specific test[10] for the N–O bond (decomposition to release nitric oxide, detected with Griess' reagent) was also positive.

These data permit the assignment of cyclic amidoxime structure **6** to the product. Some reactions of value in characterizing it are shown in Chart I. Amid-

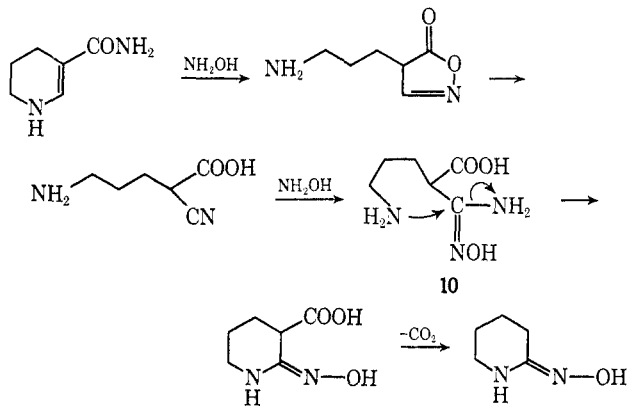
CHART I



oximes give O-acyl[11] and O-carbamoyl[12] derivatives with acid anhydrides and isocyanates, respectively, and **6** readily formed such derivatives (**7** and **8**). That O-attack had occurred was evident from the solubility of these derivatives in acid but not base, suggesting the absence of the –OH function. The nmr spectrum ($CDCl_3$) of **7** showed the ring NH signal at δ 5.58 but no signal characteristic of oxime OH (δ 8–9 ppm). Compound **8** also had an NH signal at δ 5.84 ppm, comparable to that of **7**, with a second one possibly due to the carbamate NH at δ 8.67. Amidoximes react at nitrogen with phenyl isothiocyanate to form thiourea derivatives[13] and such a product (**9**) was presumably obtained from **6**. However, its instability prevented adequate characterization.

The precursor of **6** in reactions of THNA with hydroxylamine may be 5-amino-2-cyanopentanoic acid (**4**), since this acid on reaction with hydroxylamine gave a good yield of **6**. The reaction of a nitrile with hydroxylamine is a standard synthetic method for amidoximes; the cyclic structure **6** may result from cyclization of a linear amidoxime (**10**) initially formed from **5**. Formation of **6** is therefore the end result of a complex sequence, which may be summarized as in Chart II. It

CHART II



is not known, however, if decarboxylation follows ring closure, as shown, or if the reverse sequence occurs.

Experimental Section[14]

4-(3-Aminopropyl)-2-isoxazolin-5-one (2).—A mixture of hydroxylamine hydrochloride (1.00 g, 14.4 mmol) and sodium carbonate (1.00 g, 9.4 mmol) in 20 ml of methanol was boiled for 5 min. After cooling, insoluble salts were removed by filtration and THNA (1.00 g, 7.94 mmol) was dissolved in the filtrate. After 18 hr at room temperature, the uv spectrum contained no absorption for starting material (285 mμ), but there was strong absorption at 255 mμ. Remaining inorganic materials were further precipitated by diluting with 4 ml of absolute ether, chilling for 30 min, and then filtering. This process was repeated three more times with 4-, 10-, and 15-ml portions of absolute ether. Dilution with 30 ml more of absolute ether caused precipitation of a gum. The ether–methanol layer was decanted; on further dilution with 40 ml of absolute ether, more precipitation occurred. No additional material could be obtained on additional dilution. The gum was dried under vacuum at room temperature for 4 hr, giving a dry foam (hygroscopic). The yield of **2** was 0.537 g (47.7%). In melting point determination, it became gummy at 40–50°, solidified at 95–100°, and decomposed at 170°; ir (KBr) 3600–2300 (nearly continuous, for NH_3^+), 2100, 1600 and 1500; nmr (D_2O) δ 8.00 (s, 1, H at C-3 of ring), 2.91 (t, 2, NCH_2), 1.91 (m, 4, other methylenes).

2-Acetyl-4-(3-acetamidopropyl)-3-isoxazolin-5-one (3). A synthesis of **2** in ethanol was performed. THNA (5.00 g, 39.7 mmol) and hydroxylamine hydrochloride (2.78 g, 40 mmol) were reacted directly in 95% ethanol (30 ml). After stirring for 24 hr, precipitated ammonium chloride was removed by filtration and the filtrate was stirred with sodium carbonate (2.12 g, 20 mmol) for 2 hr and then filtered. The filtrate was diluted to 50 ml with ethanol; uv measurements proved the presence of **2**. A 10-ml portion of the above isoxazolone solution was concentrated under vacuum nearly to dryness in the cold. An excess of acetic anhydride (4 ml, 42 mmol) was added to the gummy residue; a slightly exothermic reaction occurred as the gum dissolved. The flask was shaken vigorously until the mixture had cooled to room temperature. Rapid dilution with 100 ml of absolute ether caused a gum to precipitate, which was removed by filtration. Evaporation of ether from the filtrate caused precipitation of a white solid. The precipitate was recrystallized from benzene to give 0.553 g (30.5%) of **3**, sintering at 111–112° before melting at 112–113°; uv max (95% EtOH) 283 mμ (ϵ 16,700); ir (KBr) 3294 (amide NH), 1749 (ring C=O), 1717 (C=O of ring acetyl), 1641 (C=O of chain acetyl); nmr ($CDCl_3$) δ 8.40 (s, 1, H at C-3 of ring), 6.70 (broad s, 1, NH), 3.29 (apparent q, appearing as t when NH exchanged with D_2O, 2, $N-CH_2$), 2.41 (s, 3, CH_3CO

(7) C. L. Bell, C. N. V. Nambury, and L. Bauer, *J. Org. Chem.*, **29**, 2873 (1964).

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 127.

(9) K. R. Manolov, *Z. Anal. Chem.*, **234**, 37 (1968).

(10) F. Feigl and J. R. Amaral, *Mikrochim. Acta*, 337 (1958).

(11) F. Eloy, R. Lenaers, and R. Buyle, *Bull. Soc. Chim. Belges*, **73**, 518 (1964).

(12) R. Buyle, F. Eloy, and R. Lenaers, *Helv. Chim. Acta*, **46**, 1073 (1963).

(13) H. Koch, *Chem. Ber.*, **24**, 394 (1891); P. Kruger, *ibid.*, **18**, 1053. (1885).

(14) THNA was prepared as described earlier.[2] Melting points are corrected. Infrared spectra were obtained with Perkin-Elmer Model 137 or 237 spectrophotometers, uv spectra with a Beckman Model DB-G spectrophotometer, and nmr spectra with a Varian A-60 spectrometer. Gas chromatography was performed with a Varian Model 202-B instrument, using a 1/4 in. × 5 ft stainless steel column packed with SE-30 on Chromosorb W, 60–80 mesh (1:4). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich.

on ring), 1.98 (s, 3, terminal CH_3CO), 1.70–2.50 (m, other side-chain methylenes).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.38. Found: C, 53.35; H, 5.93; N, 12.24.

Hydrogenation of 4-(3-Aminopropyl)-2-isoxazolin-5-one (2).—A solution of 1.00 g (7.94 mmol) of THNA and 0.609 g (8.6 mmol) of hydroxylamine hydrochloride in 10 ml of absolute methanol was stirred with 0.465 g (4.3 mmol) of powdered sodium carbonate for 21 hr. The mixture was filtered and the filtrate (having the expected uv spectrum for **2**) was diluted to 15 ml with more methanol. Prereduced platinum oxide (0.1 g) in 15 ml of methanol was added and hydrogenation performed at atmospheric pressure and room temperature. Uptake was 305 ml (12.4 mmol) of hydrogen. That carbon dioxide was released during this process was shown by nitrogen-flushing of the gases from the hydrogenation apparatus through a saturated barium hydroxide solution; precipitation of barium carbonate occurred. The catalyst was filtered from the reaction mixture. Gas chromatography (100°) showed, in addition to solvent, only one peak (retention 2.6 min at 80 ml of He per min), which was enhanced by addition of piperidine to a small portion of the solution. The methanol filtrate was acidified with 1.5 ml of concentrated hydrochloric acid and then vacuum-evaporated, leaving a gummy solid. Redissolving in 25 ml of methanol and again vacuum-evaporating left crude piperidine hydrochloride as a solid. A portion was added to 1 ml of 6 *N* sodium hydroxide, forming an oil on the surface. Benzenesulfonyl chloride (0.5 ml) was added and the mixture stirred 2 hr. A white precipitate was removed by filtration. Its ir was identical with that of an authentic sample of N-benzenesulfonylpiperidine.

5-Amino-2-cyanopentanoic acid (4).—A solution of 2.22 g (32 mmol) of hydroxylamine hydrochloride in 20 ml of methanol was boiled for 10 min with 1.70 g (16 mmol) of powdered sodium carbonate. The mixture was cooled to room temperature and filtered and 2.00 g (15.9 mmol) of THNA was dissolved in the filtrate. The solution was refluxed for 23 hr, and then precipitated product was removed. The filtrate had uv max 212 mμ and no absorptions at 250–260 mμ for **2** or 280–290 mμ for THNA. The filtrate was evaporated to yield a second crop of product. The combined precipitates (1.94 g, 85.2%) of mp 173–175° dec were recrystallized from ethanol–water (20:3) to yield 1.23 g (54.1%) of **4**, mp 183–185° dec; ir (KBr) 3100–2600 and 2123 ($-NH_3^+$), 2247 ($C\equiv N$), 1639 and 1376 cm^{-1} ($-CO_2^-$); nmr (D_2O) δ 3.05 (t, 2, NCH_2), 1.88 (m, 4, $NCH_2CH_2CH_2$). The equiv. weight (calcd 142.1) was determined by potentiometric titrations: 142.9 with 0.0989 *N* aqueous NaOH in 85% ethanol; 142.3 with 0.0984 *N* $HClO_4$ in glacial acetic acid.

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.68; H, 7.09; N, 19.17. Found: C, 50.95; H, 7.18; N, 19.63.

Hydrolysis of 5-Amino-2-cyanopentanoic Acid (4).—A 500-mg sample of **4** was hydrolyzed by refluxing for 17 hr in 25 ml of 6 *N* hydrochloric acid. The solution was stripped of solvent *in vacuo*, and the residue was redissolved in water and evaporated again to removed residual hydrochloric acid. The residue was applied in water to an ion exchange column (Dowex 50W, X-8, H^+). After a water wash, the column was eluted with aqueous ammonia (4:1, v/v). Recrystallization from benzene–methanol gave a tacky solid, which after trituration with a small amount of methanol gave a low yield of an off-white powder, mp 150–151.5°; authentic (Aldrich Chem. Co.) 5-aminopentanoic acid (**5**) had mp 155–156° and an identical ir (KBr) spectrum. Comparative descending paper chromatography of the hydrochlorides in butanol–acetic acid–water (4:1:2) gave authentic **5**, R_f 0.51; the hydrolysis product, R_f 0.49; **4**, R_f 0.32.

Isomerization of Isoxazolone (2).—Compound **2** was first prepared from THNA (5.00 g, 39.7 mmol) and hydroxylamine hydrochloride (2.78 g, 40 mmol) in 50 ml of absolute ethanol on heating at 57° for 2 hr, and standing at room temperature for 24 hr. Precipitated ammonium chloride was filtered off and the filtrate shown to contain **2** from its uv max at 255 mμ. The solution was refluxed 15 min, then left at room temperature for 12 hr. A precipitate (1.63 g) was removed by filtration. The filtrate was refluxed again (2.5 hr), giving an additional 2.17 g of precipitate. The combined precipitates (3.80 g, 66.6%) had mp 179–180° dec and the expected ir spectrum for **4**.

Isomerization also occurred on certain manipulations of **2**. Thus, a solution of **2** prepared as above was evaporated *in vacuo* at room temperature to leave a white foamy semisolid. The solid was twice redissolved in methanol and reevaporated. It had the uv max of 255 mμ for **2**. After standing overnight at room temperature, the material became oily and only partially soluble in methanol. The methanolic mixture was filtered, the filtrate evaporated to dryness, and the residue extracted with methanol. Again insolubles were present. The combined methanol-insoluble material (0.726 g, 69.5%) had mp 175–178° dec, and was therefore shown to be **4**.

Paper Electrophoresis.—Compound **2** was prepared in methanol as in preceding experiments; after solvent-stripping, a water solution of the residue was made. A sample was applied to Whatman's No. 1 paper, along with aqueous solutions of **4** and 5-aminopentanoic acid (**5**). Electrophoresis was performed with a Beckman Model R Durrum-type instrument at 10 mA constant current for 5.5 hr in a pH 10.6 buffer (100 ml of 0.05 *M* sodium bicarbonate and 22.7 ml of 0.1 *N* sodium hydroxide). After drying at 100° for 30 min, the strips were sprayed with 30% acetic acid, redried, and then sprayed with ninhydrin. The isoxazolone (**2**) had migrated 2.6 cm (a light band at 6.8 cm was attributed to some **4**), **5** had migrated 2.9 cm, and **4**, 7.1 cm. Another strip containing **2**, without spraying, was cut at the proper location and eluted with ethanol. The solution (basic) had uv max 258 mμ; authentic **2** in dilute NaOH also had uv max 258 mμ.

2-Hydroximinopiperidine (6). Starting with THNA.—A solution of 3.0 g (43.2 mmol) of hydroxylamine hydrochloride in 5 ml of water was adjusted to pH 9 with 6 *N* NaOH, diluted with 10 ml of ethanol, and filtered. THNA (1.0 g, 7.9 mmol) was added and the solution refluxed 15 hr. A white solid deposited in the condenser, and from its ir spectrum and chemical properties was found to be ammonium carbonate (and/or bicarbonate). The solution was stripped to dryness, and the residue was extracted twice with 50-ml portions of boiling benzene. After charcoal decolorization and evaporating to 15 ml, hexane (100 ml) was added, and a solid precipitated. After chilling for 1 hr, the mixture was filtered. The residue of **6** weighed 0.29 g (32.2%), mp 120–121.5°; uv max (95% EtOH) 218 mμ (ε 6,723); ir (KBr) 3322 (NH), 3030 (broad, OH), 2891–2400 (complex, NH and OH), 1642 cm^{-1} (C=N); nmr ($CDCl_3$) δ 9.7–5.0 (very broad and shallow, 2, NH and OH), 3.20 (irregular t, 2, NCH_2), 2.27 (irregular t, 2, $N{=}CCH_2$), 1.5–2.0 (m, 4, other CH_2 groups); equiv wt (calcd 114) 115.8 from titration with $HClO_4$ in glacial acetic acid.

Anal. Calcd for $C_5H_{10}N_2O$: C, 52.63; H, 8.77; N, 24.56. Found: C, 52.74; H, 8.86; N, 24.32.

2-Hydroxyiminopiperidine (6). Starting with 5-Amino-2-cyanopentanoic Acid (4).—A solution of 1.47 g (21.1 mmol) of hydroxylamine hydrochloride in 30 ml of absolute ethanol was neutralized with a solution of 0.485 g (21.1 mmol) of sodium in 20 ml of absolute ethanol. The mixture was filtered; the filtrate was heated to reflux and treated over a 30-min period with a solution of 0.60 g (4.22 mmol) of **4** in 2 ml of water. After an additional 2 hr of reflux, the solution was evaporated to dryness and the residue was extracted with 50 ml of boiling benzene. After filtration, the volume of solution was reduced to 5 ml, and then 100 ml of petroleum ether (bp 30–60°) was added to precipitate **6**, 0.45 g (93.7%), mp 119–120°.

Qualitative Tests for Amidoxime Function in 6. N–O Bond.—A small sample of **6** in a micro test tube was thermally decomposed; the vapors impinging on a filter paper moistened with Greiss' reagent (equal portions of 1% sulfanilic acid in 30% acetic acid and 1% α-naphthylamine in 30% acetic acid) caused a pink circle, a positive test. **Amidoxime Group.**—A small amount of amidoxime in 2 ml of water was treated with 0.5 ml of 5 *M* potassium isothiocyanate and 1–2 drops of 0.1 *N* ferric nitrate. A red-brown precipitate presumed to be $Fe(amidoxime)_2SCN$ indicated a positive test. A blank solution was dark red without any precipitate.

Acid Hydrolysis of 2-Hydroximinopiperidine (6).—A solution of 200 mg of **6** in 6 ml of 3 *N* hydrochloric acid was refluxed for 3 days. Vacuum-evaporation left an oily noncrystallizing residue which was redissolved in 10 ml of absolute ethanol, diluted to 125 ml with ether, and stored overnight in a freezer. Precipitated solid was recovered and dissolved in 1 ml of water. This solution was placed on a Dowex 50W, X-8 (H^+) ion-exchange column. After a water wash, the column was eluted with aqueous ammonia (4:1, v/v). Ninhydrin-positive fractions were combined and evaporated to dryness. The solid residue was taken up in 5 ml of methanol, filtered, and evaporated to dryness. The residue was redissolved in 3 ml of water and freeze-dried. The off-white crystalline material had an ir spectrum similar to that of 5-aminopentanoic acid (**5**) but melted over a wide range (70–120°).

Extraction with 5 ml of boiling benzene left a white powdery solid having an ir spectrum now identical with that of **5** but having a low melting point (141–145°); authentic **5**, mp 155–156°. The benzene extract was evaporated to ~2 ml and then diluted to 15 ml with petroleum ether (bp 30–60°) to give a small amount of crude **6**.

2-Acetoxyiminopiperidine (7).—2-Hydroximinopiperidine (**6**) (100 mg, 0.87 mmol) dissolved exothermically in 1.0 ml of acetic anhydride. The solution was heated at 50° for 15 min, then cooled, and diluted with 20 ml of ether. A precipitate was removed and discarded. Vacuum-evaporation of the filtrate left a white granular solid which was recrystallized by dissolving it in 20 ml of ether and then diluting the solution to 100 ml with petroleum ether. Crystallization occurred on standing overnight in a freezer. The product (**7**) (51 mg, 38%) sintered at 94° and melted at 97–100°; ir (KBr) 3700–3100 (broad, NH), 1742 (C=O), 1623 cm^{-1} (C=N); nmr ($CDCl_3$), δ 5.58 (s, broad, 1, NH), 3.30 (m, 2, NCH_2), 2.38 (m, 2, $N{=}CCH_2$), 2.12 (s, 3, CH_3CO), and 1.77 ppm (m, 4, other CH_2 groups).

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.75; N, 17.94. Found: C, 53.85; H, 7.55; N, 17.88.

Phenylcarbamoyl Derivative of 2-Hydroximinopiperidine (6).—To a solution of **6** (200 mg, 1.75 mmol) in 2 ml of chloroform was added phenyl isocyanate (209 mg, 1.75 mmol) dissolved in 2 ml of chloroform. A mild exothermic reaction set in; the mixture was shaken and then allowed to stand for 1 hr. It was diluted with 10 ml of chloroform, heated nearly to boiling on a steam bath, and then diluted with petroleum ether (bp 30–60°) to a volume of 125 ml. Placing the solution in a freezer overnight caused precipitation of a white solid (309 mg, 75.7%), sintering at 134° and melting at 136–138°; uv max (95% EtOH) 237 mμ (ε 22,000); ir (KBr) 3344 and 3184 (NH), 1700 (C=O) and 1621 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.67 (broad, 1, CONH), 7.3 (m, 5, phenyl), 5.8 (broad, 1, ring NH), 3.25 (m, 2, NCH_2), 2.37 (m, 2, $N{=}CCH_2$), and 1.67 ppm (m, 4, other CH_2 groups). An analytical sample was recrystallized from ethanol–water; it sintered at 141–142° and melted at 142–143°.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.44; N, 18.03. Found: C, 61.66; H, 6.46; N, 17.87.

Registry No.—THNA, 7032-11-3; hydroxylamine, 7803-49-8; **2**, 25055-43-0; **3**, 25055-44-1; **4**, 25055-45-2; **5**, 660-88-8; **6**, 4515-19-9; **7**, 25055-48-5; **8**, 25055-49-6.

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Notes

Pyrazoles from Reaction of 3-Acetyl-1,4,5,6-tetrahydropyridine with Hydrazine and Phenylhydrazine[1]

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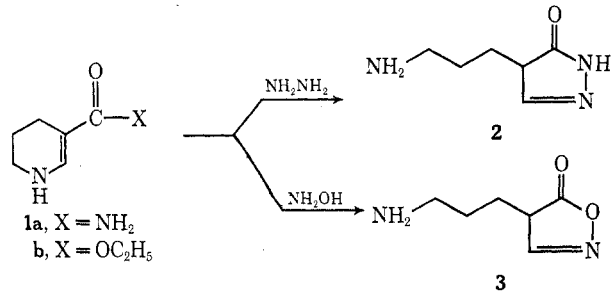
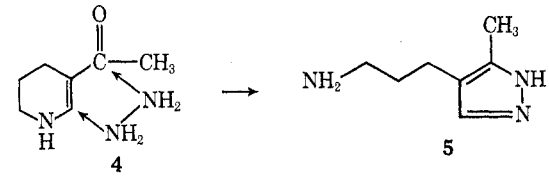
We have previously shown that 1,4,5,6-tetrahydronicotinamide (**1a**) and ethyl 1,4,5,6-tetrahydronicotinate (**1b**), which are readily available from hydrogenation of the corresponding pyridine compounds, react with binucleophiles such as hydrazine[2] and hydroxylamine[3] at both the enamino and carbonyl functions. The original ring is opened and new heterocyclic rings (pyrazolone **2** and isoxazolone **3**, respectively) are formed. In addition to nicotinic acid derivatives,



1a, X = NH_2
b, X = OC_2H_5

3-acylpyridines are cleanly reduced to the tetrahydro stage.[2,4] The reaction of hydrazine with such a keto compound should yield a pyrazole, and in this paper the formation of 3(5)-methyl-4-(3-aminopropyl)pyrazole (**5**) from 3-acetyl-1,4,5,6-tetrahydropyridine (**4**) is described.



The reaction was brought about by refluxing the reactants in aqueous alcohol. The course of the reaction was easily followed by uv spectroscopy; **4** has a strong maximum at 300 mμ, which gradually diminished as the maximum for **5** (220 mμ) developed. The product was a distillable liquid, obtained in 68% yield.

The ir spectrum of **5** contained the expected pyrazole features.[5] The terminal amino group was suggested to be strongly associated from its broad band at 3600–2400 cm^{-1}. The nmr spectrum ($CDCl_3$) had C–H signals in agreement with structure **5**. Pyrazoles generally have NH signals around 11 ppm;[5] compound **5** had only one signal (δ 5.59) other than those for C–H. The integration was not conclusive, giving a value of 2.5 H. Nevertheless, it appears that the signal is derived from protons of the amino group as well as the ring NH, presumably undergoing rapid exchange. The signal disappeared on deuteration; no other changes occurred in the spectrum.

(1) From the Ph.D. Dissertation of D. O. Pinion, Duke University, 1969.
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(5) G. Zerbi and C. Alberti, *Spectrochim. Acta*, **18**, 407 (1962); **19**, 1261 (1963).