CHEMISTRY OF 2,3,5,6-TETRAHYDRO-1-IMIDAZ(1,2-a)IMIDAZOLE[1]

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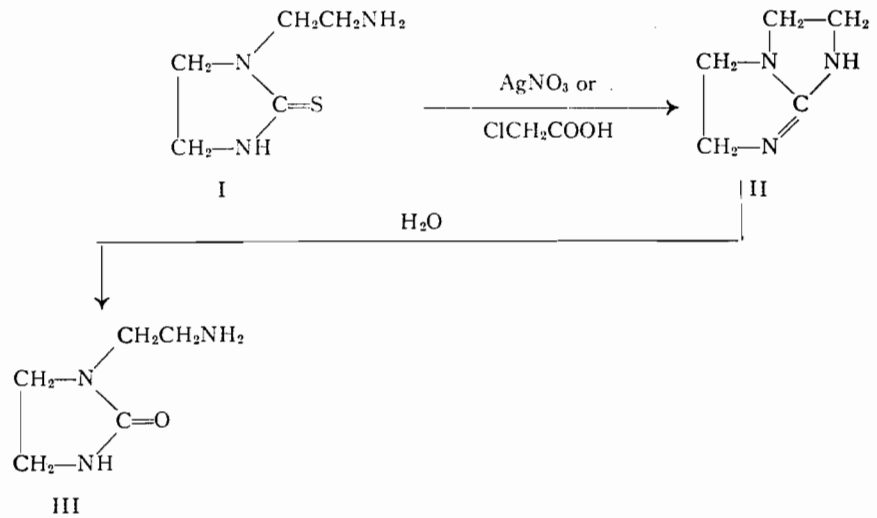
ABSTRACT

A new synthesis of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole is described. This bicyclic compound is hydrolyzed to 1-(β-aminoethyl)-2-imidazolidone. The preparation of 1-(β-hydroxyethyl)- and 1-vinyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole also is described.

Recently (5) a synthesis of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (II) from 2-(β-hydroxyethylamino)-2-imidazoline by chlorination and dehydrohalogenation was described. Compound II has now been synthesized by the simultaneous desulphurization and cyclization of 1-(β-aminoethyl)-2-imidazolidinethione (I) by silver nitrate, mercuric oxide, or preferably chloroacetic acid. When product II was isolated as its picrate the last reagent gave an 86% yield. This yield was decreased by attempting to isolate the bicyclic compound (II) as the free base. It was found later that the free base in water at room temperature hydrolyzed slowly. The hydrolysis product, 1-(β-aminoethyl)-2-imidazolidone, does not form a picrate under the conditions used for precipitation of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole as its picrate.



I II III

The preparation of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole by the reaction of ethylenediamine with cyanogen bromide was claimed by Pierron (7). A comparison of the properties of the product from ethylenediamine and cyanogen bromide with the properties of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole and 2-(β-aminoethylamino)-2-imidazoline as shown in Table I indicates that Pierron had obtained the latter compound. 2-Substituted-amino-2-imidazolines (or their tautomers) have been shown (3) to hydrolyze readily into the corresponding amine and ethyleneurea. On the other hand,

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TABLE I

COMPARISON OF 2,3,5,6-TETRAHYDRO-1-IMIDAZ(1,2-a)IMIDAZOLE WITH 2-(β-AMINOETHYLAMINO)-2-IMIDAZOLINE

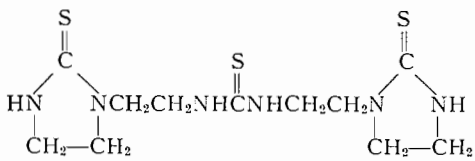
Compound	M.p. or b.p., °C. (mm.)	Picrates, m.p., °C.	Hydrolysis products
Product from cyanogen bromide and ethylenediamine[a]		203[d]	Ethylenediamine + ethyleneurea
2-(β-Aminoethylamino)-2-imidazoline (Ref. 4)	200–208 (2)[b] 188–191 (0.7)	205–206.5[d]	Ethylenediamine + ethyleneurea
2,3,5,6-Tetrahydro-1-imidaz(1,2-a)-imidazole	158.5–159.5[c]	220–221	1-(β-Aminoethyl)-2-imidazolidone

[a]*Dinitrate m.p. 138° C. (7); dihydrobromide m.p. 224° C. (7).*
[b]*Boiling point.*
[c]*Melting point.*
[d]*Dipicrates.*
[e]*Monopicrate.*

2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (II) is hydrolyzed to 1-(β-aminoethyl)-2-imidazolidone (III). Further hydrolysis of the latter compound would not be expected to yield ethylenediamine. Furthermore, 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole is monobasic while Pierron's compound is dibasic like 2-(β-aminoethylamino)-2-imidazoline.

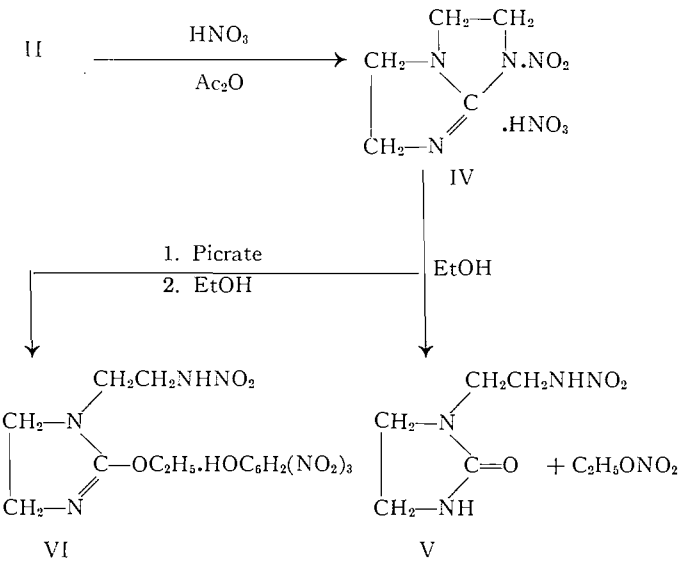
The intermediate, 1-(β-aminoethyl)-2-imidazolidinethione (I), used in the preparation of the bicyclic compound II was prepared from carbon disulphide and diethylenetriamine by the method of Hurwitz and Auten (1).

We were unable to obtain the high yields of 1-(β-aminoethyl)-2-imidazolidinethione reported; instead a mixture of 1-(β-aminoethyl)-2-imidazolidinethione, unreacted diethylenetriamine, and a compound melting at 228–229° C. was obtained. The compound melting at 228–229° C. gave analytical values in excellent agreement with those calculated for the following structure:

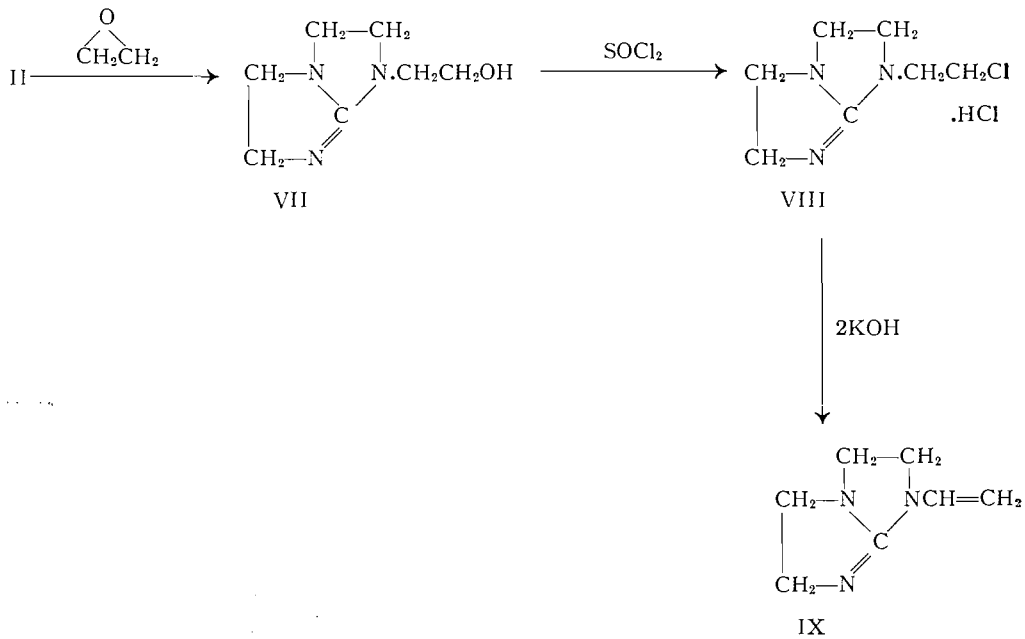


Although Hurwitz and Auten (2) claim the preparation of compounds of similar structure they do not describe their properties.

1-Nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole nitrate (IV) (5) on being refluxed with absolute ethanol gave a 76% yield of 1-(β-nitraminoethyl)-2-imidazolidone (V). The water necessary for the conversion of the bicyclic derivative (IV) into 1-(β-nitraminoethyl)-2-imidazolidone must come from the formation of ethyl nitrate. Attempts to isolate 1-(β-aminoethyl)-3-nitro-2-imidazolidone from the products of this reaction were unsuccessful. When the picrate salt of 1-nitro-2,3,5,6-tetrahydro-1-imidaz-(1,2-a)imidazole was refluxed with absolute ethanol, then the picrate (m.p. 112.5–113.5° C.) of a new compound was formed. This compound gave analytical values in agreement with structure VI.



Ethylene oxide combines with 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (II) to give 1-(β-hydroxyethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (VII). The latter compound on chlorination with thionyl chloride and dehydrohalogenation with methanolic potassium hydroxide gave 1-vinyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (IX).



EXPERIMENTAL[2]

1-(β-Aminoethyl)-2-imidazolidinethione

1-(β-Aminoethyl)-2-imidazolidinethione was prepared previously (5) in 34% yield from carbon disulphide and diethylenetriamine by the method of Hurwitz and Auten (1). It has now been prepared in 35.5% yield from thiourea and diethylenetriamine as described by Hurwitz and Auten (2). Since both these reactions gave low yields of 1-(β-aminoethyl)-2-imidazolidinethione, the reaction between carbon disulphide and diethylenetriamine was subjected to closer examination. A solution of diethylenetriamine (103 g., 1.0 mole) in benzene (250 cc.) was placed in a 3-l. three-necked flask fitted with a stirrer, dropping funnel, and thermometer. This solution was cooled with an ice bath, and carbon disulphide (76 g., 1.0 mole) in benzene (200 cc.) was added over a period of 45 minutes. After the carbon disulphide was added, the ice-water bath was replaced by a heating mantle and the reaction mixture was heated under reflux for 10 hours. It was impossible to stir the reaction mixture at the beginning of the reflux period because the solid had caked. After 1 hour at the reflux temperature the solid was converted into a dark green insoluble oil. Hydrogen sulphide was evolved throughout the entire reflux period.

After the benzene was removed *in vacuo*, the residue was extracted with absolute ethanol (3×100 cc.). The ethanol insoluble material melted at 218.5–219° C., yield 16.7 g. The ethanol filtrate was concentrated to 250 cc. and benzene (150 cc.) was added. When it had been in the refrigerator overnight, this solution deposited more crystals melting at 218–219° C., yield 3.3 g. A continuation of this method of separating the reaction products gave a total yield of 29.6 g. (18%) of product melting at 218–229° C. One crystallization from nitromethane gave material melting at 228–229° C. The material gave analytical values in good agreement with those calculated for N,N′-di-(β-1-(2-thioimidazolidinylethyl) thiourea. Anal. Calc. for $C_{11}H_{20}N_6S_3$: C, 39.73; H, 6.06; N, 25.28; S, 28.93%. Found: C, 39.80; H, 5.94; N, 25.36; S, 28.45%.

The filtrate from the high melting compound gave 86.5 g. of crude 1-(β-aminoethyl)-2-imidazolidinethione (m.p. 86–101° C.). Crystallization of this material from ethanol-benzene gave 44.9 g. (31%) of crystals melting at 109–111° C. The mother liquors from the crude 1-(β-aminoethyl)-2-imidazolidinethione on fractional distillation gave 8.8 g. (8%) of a pale yellow oil (b.p. 59° C. at 0.48 mm.). This oil gave the tripicrate of diethylenetriamine on treatment with a saturated aqueous solution of picric acid. This tripicrate melted at 210–211° C. alone and on admixture with a known sample of diethylenetriamine tripicrate (m.p. 210–211° C.).

Preparation of 2,3,5,6-Tetrahydro-1-imidaz(1,2-a)imidazole

Method A

A solution of 1-(β-aminoethyl)-2-imidazolidinethione (1.0 g., 0.007 mole) and silver nitrate (2.34 g., 0.014 mole) in 35 cc. of 85% aqueous ethanol was refluxed for 1 hour and 15 minutes. The precipitate of silver sulphide was removed by filtration. The filtrate was adjusted to a pH of 1.0 with 20% nitric acid solution and the remaining silver nitrate was precipitated as silver chloride. After the silver chloride was removed, the filtrate was evaporated to dryness. A portion (0.227 g.) of the residual oil (1.278 g.) was treated with a saturated aqueous picric acid solution. A crystalline picrate (m.p. 208–210° C.) was obtained, yield 0.197 g. One crystallization from ethanol raised the melting point

[2]*All melting points are uncorrected. The microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois.*

to 219–221° C. This picrate did not depress the melting point of a known (5) sample of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole picrate (m.p. 220–221° C.). The yield of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole based on picrate formation is 47%. A similar experiment using mercuric oxide without heating in place of silver nitrate gave a 33% yield of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole.

Method B

A solution of 1-(β-aminoethyl-2-imidazolidinethione (5.00 g., 0.034 mole) and chloroacetic acid (3.21 g., 0.034 mole) in water (100 cc.) was refluxed for 4 hours. The solution, on evaporation *in vacuo*, gave an oily residue, yield 7.2 g. An analysis of this oil for 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole by picrate formation showed that this bicyclic was formed in 77% yield. The melting point of the picrate was raised from 219° C. to 221° C. by crystallizing from water. A mixture melting point determination with 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole picrate (5) (m.p. 220–221° C.) gave no depression.

The oil (7.0 g.) was dissolved in water (160 cc.) and this solution was passed through a column (diam. 1.8 cm., length 47 cm.) of IRA-400 resin (in the hydroxyl form). The resin was washed with water (740 cc.) and the eluate and washings were evaporated to dryness *in vacuo*. This oil (4.03 g.) was dissolved in acetone and the acetone solution was cooled. The deposited crystals (m.p. 158–159° C.) were removed by filtration, yield 0.7 g. (19%). A mixture melting point determination between these crystals and a known sample of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (5) (m.p. 158.5–159.5° C.) gave no depression.

The oil obtained from the acetone mother liquors contained 46.8% 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole as determined by picrate analysis but it could not be isolated as the free base. Similar experiments gave 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole picrate in yields varying between 71 and 86%.

A sample of 1-nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole nitrate (5) (0.19 g.) was dissolved in water and treated with an aqueous solution of picric acid (15 cc.). The picrate (m.p. 145–147° C. with decomposition) was purified by one crystallization from water after which it melted at 146.5–147.5° C. with decomposition, yield 0.177 g. (53%). Anal. Calc. for $C_{11}H_{11}N_7O_9$: C, 34.28; H, 2.88; N, 25.45%. Found: C, 34.34; H, 3.12; N, 25.72%.

Reaction of 1-Nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole Nitrate in Ethanol

1-Nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole nitrate (0.57 g., 0.0026 mole) in absolute ethanol (50 cc.) was refluxed for 2½ hours. The resulting solution was concentrated to 5 cc. *in vacuo* and then stored in the refrigerator for 2 hours. The crystalline precipitate (m.p. 175° C.) was removed by filtration, yield 0.346 g. (76%). One crystallization from ethanol raised the melting point to 180° C. A mixture melting point with an authentic sample of 1-(β-nitraminoethyl)-2-imidazolidone (5) (m.p. 180–182° C.) was not depressed. The filtrate from 1-(β-nitraminoethyl)-2-imidazolidone did not yield any further identifiable products.

Reaction of 1-Nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole Picrate with Ethanol

1-Nitro-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole picrate (0.132 g.) on crystallizing three times from absolute ethanol (30 cc./g.) gave 70 mg. (47%) of a new picrate which melted sharply at 112.5–113.5° C. Anal. Calc. for $C_{13}H_{17}N_7O_{10}$: C, 36.20; H, 3.97; N, 22.74%. Found: C, 36.40; H, 4.27; N. 22.56%.

Hydrolysis of 2,3,5,6-Tetrahydro-1-imidaz(1,2-a)imidazole

2,3,5,6-Tetrahydro-1-imidaz(1,2-a)imidazole (314.8 mg., 0.003 mole) in water (5 cc.) was refluxed for 50 minutes. After the water was removed *in vacuo* the residual colorless oil (361 mg.) was dissolved in absolute ethanol (10 cc.). Gaseous hydrogen chloride was passed into this ethanolic solution until a pH of 3 was obtained. A crystalline solid was precipitated on addition of ether (5 cc.), yield 375 mg. (81%). This product melted at 175.5–177° C. alone and on admixture with a known sample of 1-(β-aminoethyl)-2-imidazolidone hydrochloride (m.p. 176–177° C.) (6). 1-(β-Aminoethyl)-2-imidazolidone does not give a picrate on addition of saturated aqueous or ethanolic solutions of picric acid. When 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole was dissolved in water at room temperature, 93% was recovered as its picrate, while after 16½ hours only 86% was recovered in this manner.

1-(β-Hydroxyethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

A solution of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (19 g., 0.17 mole) in absolute methanol (85 cc.) was treated with a solution of ethylene oxide (8.3 g., 0.188 mole) in absolute methanol (40 cc.) at 0° C. This solution was heated to reflux temperature and it was refluxed for 1½ hours. After the solvent was removed *in vacuo* under nitrogen a light yellow oil was obtained, yield 23.5 g. (89%). The oil on distillation (b.p. 125.5–126° C. at 0.13 mm.) gave a crystalline (m.p. < 60° C.) product, yield 17.4 g. Two crystallizations from ethyl acetate (*ca.* 6 cc./g.) raised the melting point to a constant value of 68.5–69.5° C. Anal. Calc. for $C_7H_{13}N_3O$: C, 54.16; H, 8.44; N, 27.06%. Found: C, 54.13; H, 8.46; N, 26.83%.

A sample of the crude waxy crystals (410 mg., 0.0026 mole) in ethyl acetate (20 cc.) was treated with a saturated ethyl acetate solution of picric acid. The crystalline picrate (m.p. 110.5–111.5° C.) was obtained in 72.4% (734 mg.) yield. Anal. Calc. for $C_{13}H_{16}N_6O_8$: C, 40.62; H, 4.20; N, 21.87%. Found: C, 40.92; H, 4.26; N, 22.06%.

Several runs on the preparation of 1-(β-hydroxyethyl)-2,3,5,6-tetrahydro-1-imidaz-(1,2-a)imidazole gave yields of pure product varying between 56 and 72%.

1-(β-Chloroethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole Hydrochloride

To 1-(β-hydroxyethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole (80 g., 0.513 mole) in absolute methanol (55 cc.) was added a 10% excess of 5 *N* HCl in methanol. The solution was taken to dryness *in vacuo* to yield a light yellow viscous oil, yield 99 g. (100%). A solution of 1-(β-hydroxyethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride (17.7 g., 0.09 mole) and freshly distilled thionyl chloride (15 g., 0.126 mole) in pure chloroform (60 cc.) was refluxed for 2 hours and 20 minutes. After the solvent and excess thionyl chloride were removed *in vacuo* under nitrogen, a semicrystalline oil was obtained, yield 19.5 g. (100%). A picrate of this oil was formed from aqueous solution in the usual manner. Two crystallizations from water raised the melting point from 117–120° C. to 120–121° C. Anal. Calc. for $C_{13}H_{15}Cl\ N_6O_7$: C, 38.76; H, 3.75; N, 20.87; Cl, 8.80%. Found: C, 38.94; H, 3.79; N, 20.48; Cl, 8.76%.

In some runs it was found that the oily product of 1-(β-chloroethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride contained 5–12% of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride. The latter compound was separated by treating the original oil with boiling acetone (11–12 cc./g.). The acetone solution on cooling deposited crystals (m.p. 153–156° C.) of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride. The melting point was raised to 156.5–157.5° C. by crystallizing from methanol. This product was identified as its picrate (m.p. 219.5–222° C.) by a mixed

melting point determination with an authentic sample (5) of 2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole picrate (m.p. 220–221° C.). The original acetone mother liquors on evaporation gave 1-(β-chloroethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride as an oil.

1-Vinyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole

1-(β-Chloroethyl)-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole hydrochloride (8 g., 0.038 mole) in absolute methanol (25 cc.) was placed in a three-necked flask fitted with a condenser, stirrer, and dropping funnel. After the solution was refluxing, methanolic potassium hydroxide solution (49.6 cc. of 1.53 *N* KOH in methanol) was added over a period of 20 minutes. After the methanolic potassium hydroxide solution was added, the dropping funnel was replaced with a capillary nitrogen lead-in. The refluxing was continued for 2 hours under nitrogen. This solution, when it was left standing under nitrogen in the refrigerator, deposited crystals of potassium chloride. The potassium chloride was removed by filtration and the filtrate was taken to dryness *in vacuo* under nitrogen. The residue was extracted with ether (5×50 cc.). Evaporation of the combined ethereal extracts gave 4.5 g. (86.5%) of a mobile light yellow oil. This product on distillation gave a colorless oil (b.p. 85.5–86° C. at 0.275 mm.). Anal. Calc. for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63%. Found: C, 60.93; H, 8.09; N, 30.83%.

A sample (233.5 mg.) of this oil in ethyl acetate (2 cc.) on treatment with a saturated ethyl acetate solution of picric acid gave 508 mg. (81%) of a crystalline picrate (m.p. 170–171.5° C.). Two crystallizations from ethyl acetate raised the melting point to 171.5–172.5° C. Anal. Calc. for $C_{13}H_{14}N_6O_7$: C, 42.63; H, 3.88; N, 22.94%. Found: C, 42.94; H, 3.91; N, 23.06%. Several preparations of 1-vinyl-2,3,5,6-tetrahydro-1-imidaz(1,2-a)imidazole gave similar results.

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