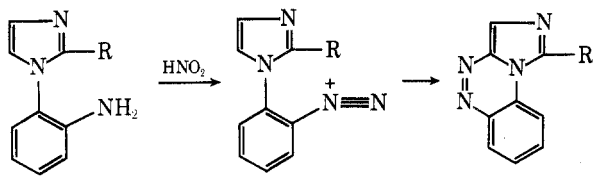
A New Example of Intramolecular 1,5-Hydrogen Transfer during Diazotization Reactions

I. Antonini, P. Franchetti, M. Grifantini,* and S. Martelli

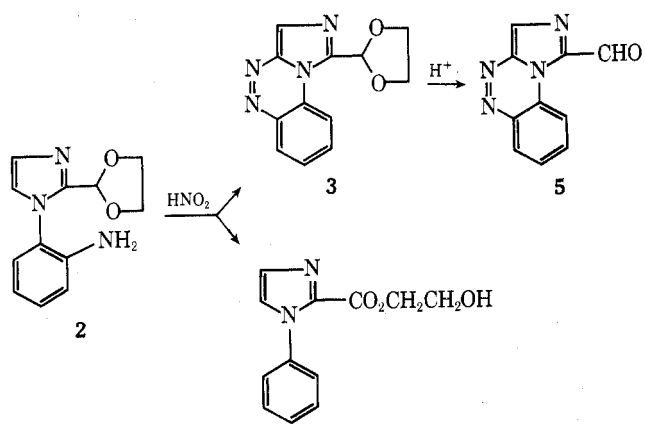
Istituto di Chimica Farmaceutica e di Chimica Organica, Università di Camerino, 62032 Camerino, Italy

Received June 11, 1975

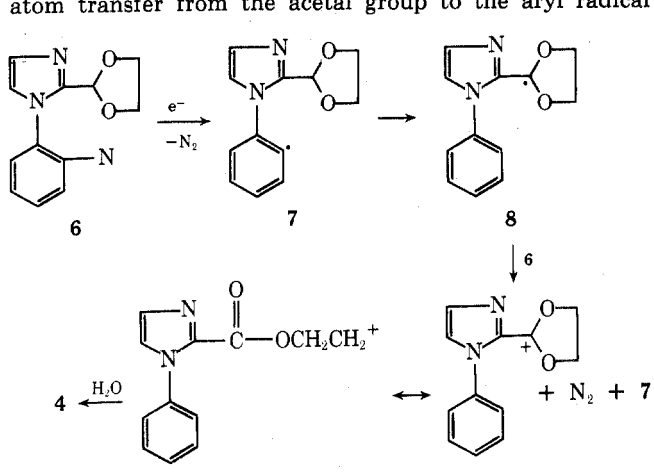
Because of a need for 1-formylimidazo[5,1-*c*]-1,2,4-benzotriazine (**5**) in other research we considered for its synthesis the method of Pozharskii and co-workers, which involved an intramolecular azo coupling of salts of *o*-(imidazolyl-1)-phenyldiazonium ion, formed by the diazotization of 1-(*o*-aminophenyl)imidazoles.[1]



Starting material was the ethylene glycol acetal of 1-(*o*-aminophenyl)-2-formylimidazole (**2**), which was readily prepared by catalytic hydrogenation of the ethylene glycol acetal of 1-(*o*-nitrophenyl)-2-formylimidazole (**1**). The diazotization reaction of **2** in diluted H_2SO_4 at 0° yields as major product (52%) the ethylene glycol monoester of 1-phenylimidazole-2-carboxylic acid (**4**) and as minor product (6%) the ethylene glycol acetal of the aldehyde **5** (**3**), from which the desired aldehyde **5** was obtained by acid hydrolysis.



The production of the ester **4** can be explained in terms of a radical chain mechanism, initiated by nitrite ion, which proceeds through an intramolecular 1,5-hydrogen atom transfer from the acetal group to the aryl radical



formed by homolytic cleavage of the C–N_2^+ bond; nucleophilic attack by water of carbonium ion **9** produced by reaction of the radical **8** with the diazonium ion **6** gives then the compound **4**.[2]

The mechanism involving radical intermediates is indicated by the adverse effect of oxygen on hydrogen transfer yields; in fact, the diazotization reaction of **2** in diluted H_2SO_4 continuously bubbled with oxygen gas gave only 35% of **4**. This compares with 52% under air.

The reduction by nitrite and intermolecular versions of this type of atom transfer are well established.[3] An example of 1,5-intramolecular hydrogen atom transfer during diazonium ion decomposition was investigated by Cohen and coworkers.[4]

In this case we have ascertained that the 1,5-hydrogen transfer is limited to acetals of type **2**; other 1-(*o*-aminophenyl)imidazol-2 derivatives such as the 1-(*o*-aminophenyl)-2-hydroxymethylimidazole and the 1-(*o*-aminophenyl)-2-methylimidazole[1] give the normal intramolecular azo coupling in high yields. The aldehyde **5** was therefore prepared in better yield by SeO_2 oxidation of 1-hydroxymethylimidazo[5,1-*c*]-1,2,4-benzotriazine (**10**) obtained by diazotization and azo coupling of 1-(*o*-aminophenyl)-2-hydroxymethylimidazole.

Experimental Section

Melting points are not corrected. NMR spectra were taken with a Jeol 60-HL spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrometer. Uv spectra were obtained with a Unicam SP 800 spectrophotometer.

1-(*o*-Nitrophenyl)-2-formylimidazole Ethylene Glycol Acetal (1). 1-(*o*-Nitrophenyl)-2-formylimidazole[5] (15.2 g, 70 mmol), ethylene glycol (25 ml), and a catalytic amount of *p*-toluenesulfonic acid were refluxed in C_6H_6 (500 ml) overnight using a Dean-Stark trap to remove the H_2O formed. The solution was cooled to room temperature, washed (aqueous Na_2CO_3), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give yellow crystals (13.1 g, 71%), mp 131–133°.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.03; H, 4.31; N, 15.89.

1-(*o*-Aminophenyl)-2-formylimidazole Ethylene Acetal (2). Compound **1** (5 g, 19.1 mmol) in 150 ml of MeOH and 5% Pd/C (1.5 g) was hydrogenated in a Parr shaker at room temperature and 10 psi pressure for 30 min. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure at 20–25° to give an oil which crystallized from EtOAc to give white needles (3.2 g, 72%), mp 123–125°.

Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.45; H, 5.88; N, 18.01.

1-Formylimidazo[5,1-*c*]-1,2,4-benzotriazine Ethylene Acetal (3) and Ethylene Glycol Monoester of 1-Phenylimidazole-2-carboxylic Acid (4). The amine **2** (4 g, 17.3 mmol) was dissolved in 80 ml of aqueous H_2SO_4 (1 *M*). The solution was cooled to below 5° with an ice bath. A cold $NaNO_2$ aqueous solution (2.6 g in 12 ml of H_2O) was slowly added with stirring to an end point with KI–starch paper. The solution was allowed to stand at room temperature for 15 min. The solution was neutralized with Na_2CO_3 and extracted with EtOAc. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column; elution with a mixture of EtOAc–MeOH (90:10) gave a first eluate containing the compound **3**. Evaporation of the solvent gave a residue which was recrystallized from EtOAc (0.25 g, 6%): mp 154–156°; uv (95% ethanol) λ_{max} 247 and 372 nm (ϵ 14800 and 5700); ir (Nujol) 1605, 1575, 1160, 1110, 765, and 760 cm^{-1}; NMR [$(CD_3)_2CO$] δ 4.28 (m, 4), 6.58 (s, 1), 7.43 (s, 1, imidazole ring proton), 7.72–8.72 (m, 4, aromatic protons).

Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.35; H, 3.91; N, 22.97.

Elution of the silica gel column with EtOAc–MeOH (80:20) gave a second eluate containing the compound **4**. Evaporation of the solvent gave a residue which was recrystallized from EtOAc (2.1 g, 52%): mp 130–132°; uv (95% ethanol) λ_{max} 260 nm (ϵ 12100); ir (Nujol) 3310 (OH), 1720 (ester C=O), 1310, 1250, 1140, 790, 765, and 695 cm^{-1}; NMR [$(CD_3)_2CO$] δ 3.30, 4.20 (two m, 4,

$-CH_2CH_2O-$), 4.60 (broad s, 1, OH), 7.40 (m, 7, aromatic and heterocyclic protons).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.02; H, 5.21; N, 12.06. Found: C, 61.83; H, 5.03; N, 11.87.

1-Formylimidazo[5,1-*c*]-1,2,4-benzotriazine (5). From 3. A solution of **3** (0.5 g, 2.3 mmol) in 5 ml of diluted H_2SO_4 was heated at 50° for 30 min. The solution was neutralized with Na_2CO_3 and extracted with EtOAc. Evaporation of the solvent gave a residue which was recrystallized from EtOH (0.27 g, 66%): mp 169–171°; uv (95% ethanol) λ_{max} 247 and 372 nm (ϵ 14700 and 5600); ir (Nujol) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.05; N, 28.27. Found: C, 60.43; H, 2.81; N, 27.95.

From 6. To 25 mmol of the alcohol **6**, dissolved in a mixture of 150 ml of dioxane and 10 ml of H_2O, 90 mmol of finely powdered SeO_2 was added. The reaction mixture was refluxed for 3 days. Se was removed by filtration; evaporation of the filtrate gave a residue which was taken up with H_2O and extracted with EtOAc. Concentration of the organic extracted left a residue which was chromatographed on a silica gel column with EtOAc as eluent. Evaporation of the first fraction of eluate gave **5** as a solid (53%).

1-Hydroxymethylimidazo[5,1-*c*]-1,2,4-benzotriazine (10). The 1-(*o*-aminophenyl)-2-hydroxymethylimidazole[5] (4 g, 19.5 mmol) was diazotized as the amine **2**. Neutralization of the solution with Na_2CO_3 gave a precipitate which was filtered, washed several times with water, and recrystallized from dioxane (3.2 g, 82%): mp 252–253°; uv (95% ethanol) λ_{max} 247, 262 (s), and 375 nm (ϵ 15600, 12700, and 5700); ir (Nujol) 3160, 1600, 1580, 1150, 1040, 770 cm^{-1}; NMR (trifluoroacetic acid) δ 5.80 (s, 2, $-CH_2-$), 7.90–9.05 (m, 5, aromatic and heterocyclic protons).

Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.71; H, 4.23; N, 27.72.

Registry No.—**1**, 56908-89-5; **2**, 56908-90-8; **3**, 56908-91-9; **4**, 56908-92-0; **5**, 56908-93-1; **6**, 56908-94-2; **10**, 56908-95-3; 1-(*o*-nitrophenyl)-2-formylimidazole, 35015-98-6; ethylene glycol, 107-21-1; 1-(*o*-aminophenyl)-2-hydroxymethylimidazole, 35016-01-4.

References and Notes

(1) A. F. Pozharskii, A. M. Simonov, and L. M. Sitkina, *Khim. Geterotsikl. Soedin.*, **5**, 916 (1969).
(2) We are grateful for the suggestion of this mechanism by one of the reviewers.
(3) H. Zollinger, *Acc. Chem. Res.*, **6**, 335 (1973), and references cited therein.
(4) T. Cohen, K. W. Smith and M. D. Swerdloff, *J. Am. Chem. Soc.*, **93**, 4303 (1971), and references cited therein.
(5) A. M. Simonov and I. G. Uryokina, *Khim. Geterotsikl. Soedin.*, 570 (1971); *Chem. Abstr.*, **76**, 25242n (1972).

A New Synthesis of L-2-Amino-3-oxalylaminopropionic Acid, the *Lathyrus sativus* Neurotoxin[1]

Betty E. Haskell* and Stephen B. Bowlus

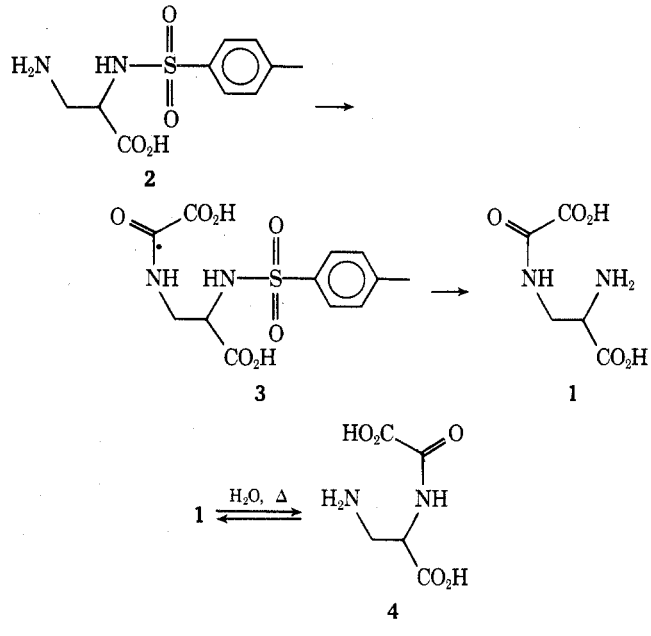
Department of Food Science, University of Illinois, Urbana, Illinois 61801

Received June 17, 1975

The nonprotein amino acid L-2-amino-3-oxalylaminopropionic acid (**1**) has been suggested[2] to be the neurotoxic principle of the legume *Lathyrus sativus*, consumption of the seeds of which is involved in the etiology of human neurolathyrism.[3] Recent studies indicate that the material is a potent antagonist of L-glutamic acid. The neurotoxin has been shown to inhibit glutamate uptake into certain yeasts[4] and into mitochondria,[5] and to block the physiological mechanism for inactivation of glutamate at the neuromuscular junction of the fleshfly *Sarcophaga bullata*,[6] a synapse at which glutamate is the putative neurotransmitter.

Our continuing investigations in the biochemistry and pharmacology of this material required the development of an efficient and economical source of the neurotoxin. The compound may be obtained in reasonable yields by isolation from seeds of *L. sativus;* the procedure is at best inconvenient and the seed, which must be imported from India, is not generally available. Previous investigations[2,4] have used simple syntheses of the material from the copper chelate of L-2,3-diaminopropionic acid and various oxalate esters. These procedures are economically prohibitive on any reasonably large scale owing to poor yields and the high cost of the starting material.

The synthesis devised in this laboratory starts with L-asparagine, the conversion of which to L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid (**2**) via Hofmann degradation of *p*-toluenesulfonyl-L-asparagine[7] has been described.[8] It was found that the utmost care must be exercised to achieve the reported[8] yield for this reaction. An effort to improve the yield of the degradation was unsuccessful: the oxidative rearrangement of amides with lead tetraacetate[9] has been reported to give Hofmann-like products in exceptional yields. At our hands, however, the reaction failed: oxidation of *p*-toluenesulfonyl-L-asparagine in the prescribed manner[9] gave *p*-toluenesulfonamide as the only identifiable product. The oxalylation of **2** proceeds smoothly in dioxane solution, and good yields of **3** are obtained after only the most cursory purification.



Several attempts to remove the toluenesulfonyl blocking group were unsuccessful. Reduction in the usual fashion with sodium and liquid ammonia[10] gave a complex mixture from which the toxin could be isolated in yields of only 2–4%. An alternative method, reduction with sodium naphthalene in tetrahydrofuran,[11] was investigated in some detail, but was equally fruitless. Our attention then turned to a less generally approved procedure, cleavage with hydrobromic acid in acetic acid.[12] This method has failed to obtain wide use in peptide chemistry since the conditions are sufficiently vigorous to cleave peptide bonds. In the present case, it was a method of last resort inasmuch as the desired product **1** is known[13] to convert to the isomeride **4** upon heating in aqueous and presumably other protic media.

The reaction proved to proceed smoothly at 70° to give moderate yields (45–50%) of **1**. As anticipated, there was also formed 2,3-diaminopropionic acid, which has been isolated in yields of up to 23%. The isomerization **1** → **4**, however, was not observed. In retrospect it is clear that the strongly acidic medium essentially irreversibly protonates