$-CH_2CH_2O-$), 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.

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

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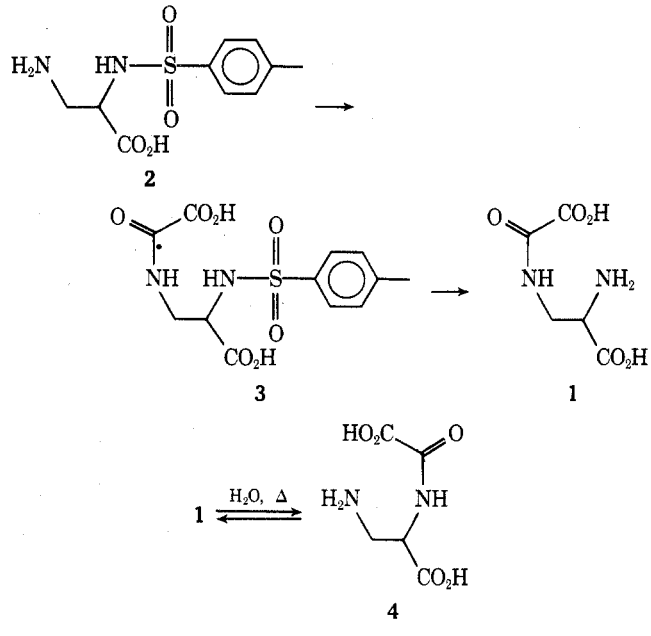
Received June 17, 1975

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

the amino group as it is formed, thus preventing nucleophilic attack of the amino group on the oxalyl carboxyl group, presumably the first step in the isomerization.

The neurotoxin prepared by this method is identical in all respects with previously reported material,[2] except for the specific rotation. We have observed $[\alpha]^{24}D$ −19.5° (*c* 2.72, 4 *N* HCl) *vs.* a reported[2] $[\alpha]^{27}D$ −36.9° (*c* 0.66, 4 *N* HCl). Previous workers have given no indication of problems of racemization in the first steps used in our preparation and we have found no change in the rotation when the final cleavage reaction is conducted over periods of 2–16 hr, and at temperatures of up to 100°. Moreover, a sample isolated from *L. sativus* seeds by the reported procedure[2] gave at our hands $[\alpha]^{24}D$ −15.4° (*c* 3.00, 4 *N* HCl). We therefore suggest that the previously reported value is in error.

Experimental Section[14]

L-3-Oxalylamino-2-(*p*-toluenesulfonyl)aminopropionic Acid (3). To a chilled solution of oxalyl chloride (35 ml, 0.4 mol) and 400 ml of dry dioxane was added with vigorous stirring L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid (25.8 g, 0.1 mol). The mixture was stirred for 6 hr at room temperature, and the reaction was then quenched by the slow addition of chipped ice. The mixture was evaporated to a small volume, and the oily residue was dried in vacuo. After trituration with dichloromethane, the tarry product slowly solidified. The solid was crushed and washed with additional dichloromethane. There was obtained 27.1 g (82%) of a pale tan powder: mp 187–189° dec; $[\alpha]^{23}D$ +18.1° (*c* 3.00, methanol); ir (Nujol) 3180, 3130, 1680, 1530, 1235, 1205, 1155, 1080, 955, 817, 745, 714, and 650 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_2O_7S$: C, 43.64; H, 4.27; N, 8.48; S, 9.64. Found: C, 43.57; H, 4.44; N, 8.55; S, 9.59.

A sample of the product (ca. 500 mg) was stirred overnight with 50 ml of methanolic hydrogen chloride (1.25 *N*). The solvent was removed and the residue was crystallized from dichloromethane–petroleum ether (bp 30–60°) to afford the dimethyl ester: mp 113–114.5°; NMR 7.5 (center of AA'BB' pattern, 5 H, aryl and amide H), 5.77 (d, 1 H, J = 7.5 Hz, sulfonamide H), 4.07 (m, 1 H), 3.88 (s, 3 H), 3.68 (m, 2 H), 3.62 (s, 3 H), and 2.40 ppm (s, 3 H).

Anal. Calcd for $C_{14}H_{18}N_2O_7S$: C, 46.92; H, 5.06; N, 7.82; S, 8.95. Found: C, 47.14; H, 5.09; N, 7.87; S, 8.75.

L-2-Amino-3-oxalylaminopropionic Acid (1). A thick-walled pressure bottle was charged with L-3-oxalylamino-2-(*p*-toluenesulfonyl)aminopropionic acid (5.9 g, 18 mmol), phenol (5.2 g), and 100 ml of 32% hydrogen bromide in acetic acid. The bottle was firmly stoppered, and the mixture was heated for 8 hr at 70°. The bottle was then chilled on ice, and the mixture was poured into ca. 600 ml of dry ether. The mixture was chilled for several hours, and the precipitated solids were collected and were washed with additional ether. The hygroscopic product was taken up in water, the solution was filtered with charcoal, and the filtrate was percolated through a 2.5 × 40 cm bed of Dowex 1 × 8 (formate). The column was washed with 1000 ml of water, which was discarded. The product was eluted with 2.5% formic acid; the ninhydrin-positive fractions were pooled and lyophilized. The residue was washed with a small amount of chilled water and acetone, and was air dried to give 1.70 g (49%) of the desired product as the hydrate, mp 206° (dec with gas evolution), $[\alpha]^{24}D$ −19.5° [*c* 2.72 (anhydrous basis), 4 *N* HCl] [lit.[2] $[\alpha]^{27}D$ −36.9° (*c* 0.66, 4 *N* HCl)].

Anal. Calcd for $C_5H_8N_2O_5 \cdot H_2O$: C, 30.93; H, 5.19; N, 14.43. Found: C, 30.92; H, 5.15; N, 14.35.

This material was found to be indistinguishable from the natural product isolated by the method of Rao et al.,[2] by chromatography, electrophoresis, and ir. The ir spectra were identical with the published spectrum.[2] The two materials had equal potency when assayed[4] as inhibitors of glutamate transport into yeast cells.

Registry No.—**1**, 5302-45-4; **2**, 21753-19-5; **3**, 57016-83-8; **3**, dimethyl ester, 57016-84-9; oxalyl chloride, 79-37-8; hydrogen bromide, 10035-10-6.

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Isolation and Alkaline Decomposition of the Intermediate Pyridinium Salts Occurring in the Pyridine *N*-Oxide Oxidation of α-Halo Esters or Acids

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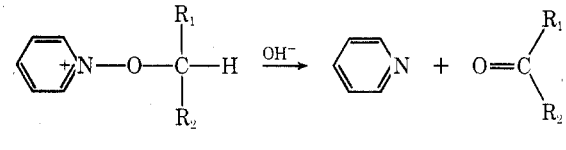
Received July 11, 1975

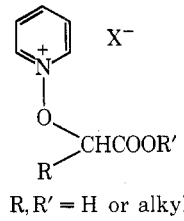
1-Alkoxypyridinium salts are well known; they result from nucleophilic substitution by pyridine *N*-oxide upon alkyl halides, sulfates, or sulfonates and oxonium salts.[1a] Their reactivity toward nucleophiles has been studied by Katritsky et al.[2] In basic solution these salts decompose to a carbonyl compound and the parent pyridine[3] as shown in Scheme I. This reaction can be used either as a carbonyl

Scheme I



compound preparation[1b,4] or as a way of deoxygenating pyridine *N*-oxide in nonreducing conditions.[5]

1-Alkoxypyridinium salts bearing an acid or ester function at the α position of the alkoxy group, such as **1** have not been described yet (though some derivatives of 1-[4-

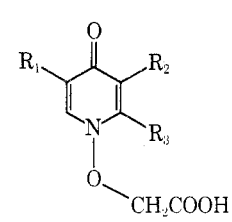


R, R' = H or alkyl

1a, X = Br

b, X = NO_3

c, X = picrate



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