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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(1) Supported by a grant (NS 08947) from the National Institute of Neurological Disease and Stroke.
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(14) Melting points were determined on a Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded in deuteriochloroform solution on a Varian HA-100 spectrometer; chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ scale). Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Optical rotations were measured in a 1-dm cell on a Zeiss circle polarimeter 0.01°. Microanalyses were performed by J. Nemeth and associates in the Department of Chemistry, University of Illinois. Hydrogen bromide (30–32% in acetic acid) was obtained from Eastman. L-Asparagine hydrate was purchased from Ajinomoto Co., Inc., Tokyo. The preparations of *p*-toluenesulfonyl-L-asparagine and L-3-amino-2-(*p*-toluenesulfonyl)aminopropionic acid were by established methods.

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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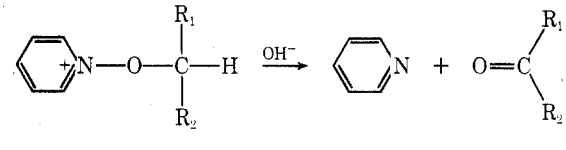
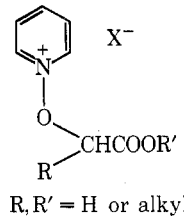
1-Alkoxypyridinium salts are well known; they result from nucleophilic substitution by pyridine *N*-oxide upon alkyl halides, sulfates, or sulfonates and oxonium salts.[1a] Their reactivity toward nucleophiles has been studied by Katritsky et al.[2] In basic solution these salts decompose to a carbonyl 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

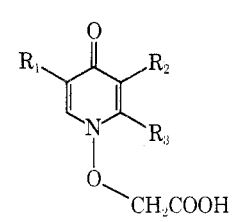


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Table I
Reaction of α-Bromo Esters and Acids, RCHBrCOOR′, with Pyridine N-Oxide → Py⁺—ORCHCOOR′X⁻

		X = Br			X = NO_3			NMR of nitrates, ppm						X = picrate
R	R′	Compd	Yield, %	Mp, °C[a]	Compd	Yield, %	Mp, °C[a]	H	R	R′	α	β	γ	Mp, °C[a]
H	Me	**3a**	78	74.5	**3b**	82[b]	Oil	5.5 s		3.85 s	9.4	8.3	8.75	118
H	*t*-Bu	**4a**	31	*c*	**4b**	60	116	5.3 s		1.5 s	9.3	8.23	8.7	118.5
H	CH_2Ph	**5a**	33	*c*	**5b**	43	104	5.5 s		5.3 s 7.47 s	9.34	8.29	8.74	101.5
Me	Me	**6a**	49	*c*	**6b**	81[b]	Oil	5.6 q	1.8 d	3.85 s	9.32	8.25	8.72	112
Ph	Me				**7b**	50	109	6.5 s	7.5 s	3.86 s	9.13	8.15	8.66	110
H	H	**8a**	62	107	**8b**	55	129	5.43 s			9.4	8.28	8.74	140
Ph	H	**9a**	89	103.5	**9b**	45	115	6.22 s	7.48 s		8.98	8.02	8.52	122

[a] Melting with decomposition. [b] Yield of picrate. [c] Hygroscopic crystals.

Table II
Reaction of α-Bromoacetic Acid with N-Oxides of Substituted Pyridines in the Presence of $AgNO_3$

				NMR, ppm				
Compd	Substituent	Yield, %	Mp, °C[a]	$-CH_2-$	α	β	γ	$-CH_3$
10b	2-Me	55	124	5.37	9.30	8.05	8.55	2.97
11b	3-Me	59	129	5.37	9.16	8.10	8.53	2.62
12b	4-Me	62	129	5.34	9.10	8.02		2.73
13b	2,6-Di Me	50	132	5.17		7.88	8.34	2.90

[a] Melting with decomposition.

oxo-1(*H*)-pyridyl]oxyacetic acid are known,[6] these compounds **2** possess the structure of neutral N-substituted pyridone, but not that of a pyridinium salt).

Nevertheless, the functional salts **1** have been postulated as intermediates in the oxidation of ethyl α-bromoacetate[7] or in the oxidative decarboxylation of either α-halo acids[8] or carboxylic anhydrides[9,10] by means of pyridine *N*-oxide. Reported attempts to isolate such quaternary salts derived from α-halo esters have not been successful,[7] though functional 1-alkoxypyridinium salts have been isolated in other cases, as, for example, in the reaction of α-picoline *N*-oxide with phenacyl bromide.[11]

We wish to report in the present note a convenient procedure for the preparation of the salts **1** and the results of their alkaline degradation.

The isolation of these salts as relatively stable crystalline solids in fairly good yields (see Table I) can be achieved by performing the reaction at 0°. Higher temperature must be avoided, because these compounds are very sensitive to nucleophiles.[2]

α-Bromo esters react in the cold with pyridine *N*-oxide, provided that the former is not fully substituted at the α position. The reaction is facilitated by means of silver nitrate; in this case, pyridinium nitrates which are more easily crystallized are obtained. The latter, having a less nucleophilic anion than the bromides, are more stable, and can be recrystallized from acetone without noticeable decomposition, while, for example, the bromide **3a** undergoes under these conditions a decomposition to methyl bromoacetate and pyridine *N*-oxide.

In the case of the derivatives **7b** the bromide is too unstable to be isolated and the nitrate slowly decomposes to methyl phenylglyoxylate. When bromides or nitrates could not be obtained or when they were too hygroscopic, the pyridinium picrates, which have proved to be more stable, were isolated.

The reaction of pyridine *N*-oxide with α-bromo acids is slower than the reaction with the corresponding esters. Nevertheless, the bromides **8a** and **9a** could be isolated in respectively 62 and 80% yield after 7 days at 4°. In this case too, it is more convenient to prepare the nitrates by working in the presence of silver nitrate.

Table III
Decomposition of Nitrates 4b, 5b, and 7b by Triethylamine in Methanol

Compd	Pyridine yield, %[a]	α-Carbonyl ester yield, %[b]
4b	97.5	97
5b	97.5	89
7b	95	95

[a] Determined by VPC analysis. [b] Gravimetric determination of the 2,4-DNP.

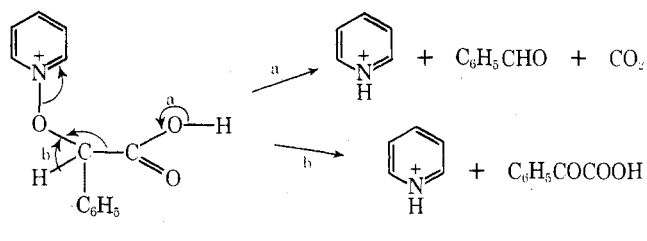
This reaction has been extended to the *N*-oxides of picolines and 2,6-dimethylpyridine as shown in Table II.

The reaction of quaternary salts **4b, 5b,** and **7b** with aqueous 1 *N* sodium hydroxide at room temperature produced pyridine in excellent yield (respectively 97, 95, and 92% in pyridinium picrate) but the resulting α-keto esters were not isolated owing to their hydrolysis by the basic medium.

Best yields of α-carbonyl esters (isolated as 2,4-DNP) are realized by decomposition of the salts with triethylamine in methanolic solution at ambient temperature (see Table III). In the case of the unstable nitrate **7b** this decomposition can take place slowly in the solid state, as previously stated.

Cohen and Song[8] have shown that decomposition of α-halo acids by pyridine *N*-oxide in refluxing benzene, toluene, or xylene is mainly an oxidative decarboxylation (path a in Scheme II) for which they have postulated the intermediacy of salts such as **1**. For example, in the reaction of

Scheme II



excess pyridine *N*-oxide with α-bromophenylacetic acid in refluxing benzene, they obtained principally benzaldehyde (49%) and carbon dioxide (46%); only a small amount (5%) of phenylglyoxylic acid was produced.

In our hands, the salt **9b**, upon treatment by aqueous 1 *N* sodium hydroxide at room temperature, reacted mainly according to path b of Scheme II, providing pyridine (78%), phenylglyoxylic acid (70% as mercuric salt), benzaldehyde (2.5%), and carbon dioxide (2.1%).

Similarly, Cohen and Song obtained formaldehyde (65%) and carbon dioxide (100%) by refluxing in xylene a mixture of chloroacetic acid and pyridine *N*-oxide, while the decomposition of the salt **8b** that we performed in aqueous sodium hydroxide yielded up to 37% of glyoxylic acid (determined as calcium oxalate after subsequent oxidation).

The decomposition of the salt **7b** was performed on a batch scale in order to show the potential utility of these salts for α-keto ester synthesis. The intermediate pyridinium salt was not isolated and the reaction was performed in three different modes (see Experimental Section): (1) in equimolecular ratio without silver nitrate, (2) with an excess of pyridine *N*-oxide (1.5–1) and without silver nitrate, (3) in the presence of silver nitrate in equimolecular ratio.

The first two reactions were carried out in boiling methylene chloride while the third one was done in cold acetonitrile followed by fast treatment with triethylamine.

Yields of isolated methyl phenylglyoxylate were respectively (1) 48%, (2) 65%, and (3) 87%. So, this third procedure (3) can be recommended for α-keto ester synthesis from α-bromo esters under very mild conditions; it seems advantageous over the dimethyl sulfoxide oxidation process which has been applied to ethyl bromoacetate by Hunsberger and Tien,[12] and which is not free from side reactions. Although this method has been shown to give ethyl glyoxylate in 70–75% yields, the results were unsatisfactory with *tert*-butyl bromoacetate as reported by Carpino,[13] who isolated only small amounts of the phenylhydrazone of *tert*-butyl glyoxylate.

In conclusion, we show that the intermediate salts produced in the first step of the oxidation of α-halo acid or ester by pyridine *N*-oxide can be isolated; in addition the acid salts can be decomposed in a way that is different from the usual one which has been described in the decarboxylative process. Furthermore the ester salts may be useful intermediates in α-carbonyl ester synthesis.

Experimental Section

The products described in Tables I and II were prepared by one of the following methods. Yields were not optimized and melting points (open capillary) are uncorrected. NMR spectra were obtained on a Jeol C60HL instrument in D_2O solution using TSP (sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$) as internal standard. Chemical shifts are reported in parts per million (δ) and are followed by a letter giving the spin multiplicity except for the α, β and γ protons of the pyridine, which give rise to multiplets.[14] Satisfactory analytical data (±0.3% for C, H, N) were reported for the nitrates **4b, 5b, 7b, 8b, 10b, 11b, 12b,** and **13b** and for the picrates issued from **3b, 6b,** and **9b.**

General Procedure for the Conversion of α-Bromo Esters to 1-(1-Alkoxycarbonylalkoxy)pyridinium Bromides 3a–6a. To a solution of pyridine *N*-oxide (0.02 ml) in CH_2Cl_2 (5 ml) cooled to 0°C was added 0.02 mol of α-bromo ester. The mixture was kept at 4°C during 48 hr. In one case (**3a**) crystals appeared spontaneously; they were collected by filtration and washed with ether. In the other cases, crystallization was initiated by adding small amounts of ether.

General Procedure for the Conversion of α-Bromo Acids to the 1-(1-Carboxyalkoxy)pyridinium Bromides 8a and 9a. To a solution of pyridine *N*-oxide (0.02 mol) in CH_2Cl_2 (5 ml) cooled to 0°C was added 0.02 mol of α-bromo acid; the mixture was kept at 4°C during 7 days. Crystals appeared spontaneously; they were collected by filtration and washed with CH_2Cl_2.

General Procedure for the Conversion of α-Bromo Esters to the 1-(1-Alkoxycarbonylalkoxy)pyridinium Nitrates 3b–7b. Pyridine *N*-oxide (0.05 mol) and $AgNO_3$ (0.05 mol) were dissolved in 20 ml of CH_3CN under cooling (down to 0°C). To the stirred solution, 0.05 mol of bromo ester dissolved in 10 ml of CH_3CN was added over a period of 0.5 hr. The mixture was stirred for an additional 24 hr at room temperature (only 4 hr for **7b**). After filtration the precipitated AgBr was washed with acetonitrile. Adding small amounts of ether to the filtrate caused the precipitation of the pyridinium salt, which was collected by filtration and recrystallized from acetone or a mixture of acetone–acetonitrile.

When the nitrates were precipitated as oily products, they were transformed into picrates by treatment with an ethereal solution of picric acid.

General Procedure for the Conversion of α-Bromo Acids to the 1-(1-Carboxyalkoxy)pyridinium Nitrates 8b and 9b. Bromo acid (0.05 mol) dissolved in 20 ml of CH_3CN was added with stirring to a cooled solution of pyridine *N*-oxide (0.05 mol) and $AgNO_3$ (0.05 mol) in 10 ml of acetonitrile. The mixture was stirred for an additional period of 3 hr for **9b** and 24 hr for **8b.** The crystals thus obtained (AgBr and the pyridinium salt) were collected by filtration and washed with aqueous acetonitrile (5–10% H_2O). The filtrate was evaporated under vacuum and the residual product recrystallized from CH_3CN which contained traces of water.

The same procedure was applied to *N*-oxides of substituted pyridines listed in Table II, the additional stirring period being 24 hr.

Decomposition of the Ester Salts 4b, 5b, and 7b by 1 *N* Sodium Hydroxide. A solution of the salt **7b** (1.53 g, 5 mmol) in 50 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 0.5 hr at room temperature. One-half of the solution was extracted with chloroform (3 × 10 ml). The chloroform extract treated with an ethereal solution of picric acid gave 0.711 g (92%) of pyridinium picrate, mp and mmp 165° after recrystallization from EtOH.

To the second half of the initial solution was added a sulfuric solution of 2,4-dinitrophenylhydrazine and the precipitated 2,4-DNP was isolated in the usual manner. TLC analysis on silica gel showed that this 2,4-DNP was not the derivative of the expected α-keto ester but that of the keto acid resulting from hydrolysis as was confirmed by its melting point, 195–196° (lit.[15] 196–197°).

The same procedure applied to the salt **4b** and **5b** gave respectively a 97 and 95% yield of pyridinium picrate.

Decomposition of the Ester Salts 4b, 5b, and 7b by Triethylamine in Methanol. A 20-ml solution of 1.53 g (5 mmol) of **7b** and 14 ml (10 mmol) of triethylamine was allowed to stand for 0.5 hr at room temperature.

A 10-ml portion of the initial solution was extracted with chloroform (3 × 10 ml); quantitative VPC analysis of an aliquot of the extracts indicated a 95% yield of pyridine.

A 5-ml portion of the initial solution was added to a sulfuric solution of 2,4-dinitrophenylhydrazine. The methyl phenylglyoxylate 2,4-DNP (0.409 g, 95%) was isolated as usual and recrystallized from a mixture of AcOEt–EtOH, mp and mmp 172° (lit.[16] mp 171°).

The same procedure applied to **4b** gave a 97.5% yield in pyridine and a 97% yield in *tert*-butyl glyoxylate 2,4-DNP (0.387 g), mp 116.5°.

Under the same conditions, **5b** afforded a 97.5% yield in pyridine and an 89% yield in benzylglyoxylate 2,4-DNP (0.384 g), mp 191° (lit.[17] mp 190–192°).

Decomposition of 1-(1-Carboxymethoxy)pyridinium Nitrate (8b) by 1 *N* Sodium Hydroxide. A solution of 1.08 g (5 mmol) of **8b** in 50 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 14 hr. Extraction with chloroform (3 × 10 ml) followed by treatment of the chloroform extract by ethereal picric acid gave 1.25 g (82%) of pyridinium picrate, mp and mmp 165°.

The aqueous solution was then refluxed for 1 hr, allowing the formation of oxalic acid by quantitative oxidation of glyoxylic acid. The cooled solution was then acidified by addition of 10% AcOH. Calcium chloride (0.1 *N*, 100 ml) was added and the resulting mixture was heated with a steam bath for 0.5 hr. The calcium oxalate precipitated was isolated by filtration, washed with water, and dissolved in 100 ml of 10% sulfuric acid. The amount (1.72 mmol, 34.5%) was determined by permanganic titration.

Decomposition of 1-(1-Carboxybenzyloxy)pyridinium Nitrate (9b). A solution of 1.46 g (5 mmol) of **9b** in 20 ml of aqueous 1 *N* sodium hydroxide was allowed to stand for 0.5 hr. Barium carbonate precipitated by addition of 30 ml of aqueous 0.2 *M* barium hydroxide was isolated by filtration, washed with water, and dis-

solved in dilute HCl; sodium sulfamate was added to the chlorhydric solution and the precipitated barium sulfate was isolated as usual. From the amount of barium sulfate obtained (0.0243 g) a 2.1% yield in carbon dioxide was calculated.

The filtrate was then extracted by chloroform (3 × 10 ml) and the combined extracts were diluted to 50 ml. Treatment of 20 ml of this solution by ethereal picric acid gave 0.480 g (78%) of pyridinium picrate, mp and mmp 165° after recrystallization from EtOH; the benzaldehyde content of the above solution was determined by quantitative VPC analysis, which indicated a 2.5% yield.

The remaining aqueous layer was then acidified with dilute HCl and extracted with ether (3 × 10 ml). The residue from evaporation of ether was dissolved in water (10 ml) and an aqueous solution of mercuric acetate was added to the resulting solution. The mercuric salt of phenylglyoxylic acid which precipitated was isolated by filtration, washed, and dried; the salt weighed 0.86 g (70%) and had mp 167° (lit. mp[8] 165–166°).

Preparation of Methyl Phenylglyoxylate. A. By Reaction of Methyl α-Bromophenylacetate with 1 Equiv of Pyridine *N*-Oxide. A solution of pyridine *N*-oxide (5.25 g, 55 mmol) and methyl α-bromophenylacetate (11.9 g, 55 mmol) in methylene chloride (10 ml) was refluxed for 2 hr; 100 ml of a 10% HCl solution was added and the resulting mixture was extracted with ether (3 × 50 ml). Evaporation of the dried extract (Na_2SO_4) and distillation of the oily residue afforded 4.2 g (48%) of methyl phenylglyoxylate, bp 66° (0.5 mm), 2,4-DNP mp 172° (lit.[16] mp 171°).

B. By Reaction of Methyl α-Bromophenylacetate with 1.5 Equiv of Pyridine *N*-Oxide. A solution of pyridine *N*-oxide (10.5 g, 111 mmol) and methyl α-bromophenylacetate (16.8 g, 73 mmol) in methylene chloride (20 ml) was refluxed for 2 hr (TLC examination showed that methyl α-bromophenylacetate had been completely transformed); work-up as above afforded 7.86 g (65%) of methyl phenylglyoxylate.

C. By Reaction of Methyl α-Bromophenylacetate with Pyridine *N*-Oxide in the Presence of Silver Nitrate and Subsequent Decomposition by Triethylamine. A solution of methyl α-bromophenylacetate (17 g, 75 mmol) in acetonitrile (15 ml) was added dropwise, under stirring, to an ice-cooled solution of pyridine *N*-oxide (7.4 g, 78 mmol) and silver nitrate (13.3 g, 78 mmol) in acetonitrile (30 ml). Stirring was continued for an additional 2 hr; the precipitated silver bromide was eliminated by filtration and washed with acetonitrile. To the stirred filtrate, triethylamine was slowly added, and the resulting solution was then acidified by 10% HCl. Work-up as in A afforded 10.8 g (87%) of methyl phenylglyoxylate.

Registry No.—**3a**, 56943-39-6; **3b**, 56943-41-0; **3c**, 56943-42-1; **4a**, 56943-43-2; **4b**, 56943-45-4; **4c**, 56943-46-5; **5a**, 56943-47-6; **5b**, 56943-49-8; **5c**, 56943-50-1; **6a**, 56943-51-2; **6b**, 56943-53-4; **6c**, 56943-54-5; **7b**, 57031-39-7; **7c**, 56943-56-7; **8a**, 56943-57-8; **8b**, 56943-59-0; **8c**, 56943-60-3; **9a**, 56943-61-4; **9b**, 56943-63-6; **9c**, 56943-64-7; **10b**, 109-06-8; **11b**, 108-99-6; **12b**, 108-89-4; **13b**, 108-48-5; methyl α-bromoacetate, 96-32-2; *tert*-butyl α-bromoacetate, 5292-43-3; benzyl α-bromoacetate, 5437-45-6; methyl α-bromopropanoate, 5445-17-0; methyl α-bromobenzeneacetate, 3042-81-7; α-bromoacetic acid, 79-08-3; α-bromobenzeneacetic acid, 4870-65-9; pyridine *N*-oxide, 694-59-7; $AgNO_3$, 7761-88-8; picric acid, 88-89-1; sodium hydroxide, 1310-73-2; 2,4-DNP, 119-26-6; triethylamine, 121-44-8; *tert*-butyl glyoxylate 2,4-DNP, 56943-65-8; methyl phenylglyoxylate, 15206-55-0.

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Lithiation of Methoxyindoles

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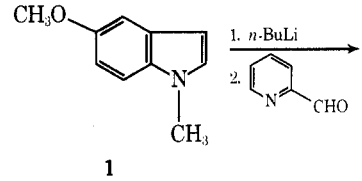
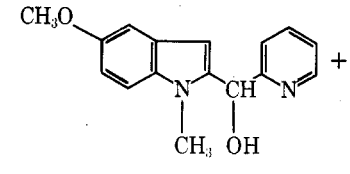
It has been demonstrated that 1-benzenesulfonylindole can be lithiated in the 2 position and that the resulting lithiated intermediate can be used for the synthesis of a variety of 2-substituted indoles.[1,2] This extends earlier studies[3] which had demonstrated selective lithiation of 1-alkylindoles, since the benzenesulfonyl group can be removed readily by hydrolysis.[1] In view of the interest in biologically active methoxyindoles we have now extended lithiation studies to 5- and 6-methoxyindole derivatives.

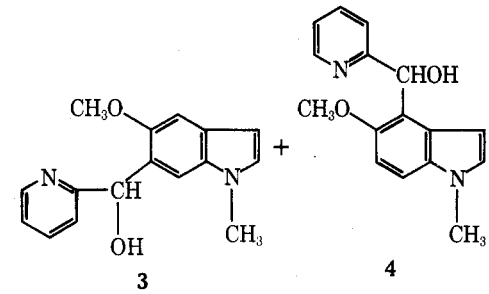
Lithiation of 1-methyl-5-methoxyindole (**1**) by *n*-butyllithium in refluxing ether was nonselective as judged by the formation of three isomeric alcohols after reaction with pyridine-2-carboxaldehyde. Two of the products (**2** and **3**) were obtained as pure crystalline compounds while a third (**4**) was obtained as an oil slightly contaminated with **2**.



1



2



3 4

Product **2** was identified as the 2-substituted product on the basis of a sharp singlet for the indole 3H proton in the NMR. The other major product was assigned structure **3** since the aromatic region reveals two prominent singlets at δ 6.96 and 7.22, indicating that both of the 5 and 6 positions of the ring are substituted. The third product was noncrystalline and a sample purified by chromatography contained ~10% **2**. However, the NMR clearly indicated that it was an isomeric product of substitution on the carbocyclic ring since the indole 3H signal appeared as a doublet and the other spectral features were those expected for a 1:1 ad-