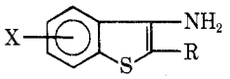
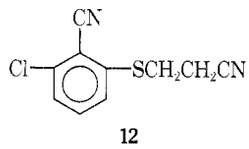
Table I
3-Aminobenzo[*b*]thiophenes[a]



Compd	X	R	Mp, °C	Yield, %	Crystn solvent[b]
1	4-Cl	CN	181–182	66	A
2	6-Cl	CN	215–216	75	A
3	4-NO_2	CN	177–179	84	A
4	4-Cl	$COCH_3$	101–103	68	B
5	4-NO_2	$COCH_3$	136–137	83	A
6	4-Cl	COC_6H_5	126–127	60	B
7	4-NO_2	COC_6H_5	139–141	60	A
8	4-Cl	$CONH_2$	225–227	69	A
9	4-NO_2	$CONH_2$	238–239	65	C
10	5-NO_2	CN	272–273	87	D
11	5-NO_2	COC_6H_5	205–207	90	C
13	H	CN	155–156[c]	70	A
14	H	$COCH_3$	147–149[d]	67	E
15	4-OCH_3	CN	173–176	50	D

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [b] A = alcohol; B = alcohol–water; C = acetonitrile; D = DMF–water; E = benzene–hexane. [c] Lit.[1] mp 155–156°. [d] Lit.[1] mp 145.5–147°.

period of time. In the second process, this problem was overcome with the use of 3-mercaptopropionitrile[9] anion. In this reaction sequence, the *o*-nitrobenzonitrile was allowed to react with the mercaptan anion in aqueous DMF containing excess potassium hydroxide. Displacement occurred rapidly at ice bath temperature, and an equilibrium mixture was formed involving the cyanoethyl thioether and the corresponding *o*-mercaptobenzonitrile anion. When the reaction was quenched soon after addition of the mercaptan, the cyanoethyl thioether could be isolated and characterized, as in the case of **12**. Addition of the alkylating



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agent and subsequent ring closure yielded the desired product. Compounds prepared by this method were 3-aminobenzo[*b*]thiophene-2-carbonitrile (**13**), 3-aminobenzo[*b*]thien-2-yl methyl ketone (**14**), and 3-amino-4-methoxybenzo[*b*]thiophene-2-carbonitrile (**15**).

These two procedures provide a convenient, rapid route to 3-aminobenzo[*b*]thiophenes, substituted at the 2 position with cyano, acyl, or carboxamido functions, from readily available *o*-nitrobenzonitriles.

Experimental Section[10]

Materials. 2-Chloro-6-nitrobenzonitrile, 4-chloro-2-nitrobenzonitrile, 2-chloro-5-nitrobenzonitrile, and *o*-nitrobenzonitrile were commercially available. 2,6-Dinitrobenzonitrile[7] and 6-nitro-*o*-anisonitrile[11] were prepared by procedures described in the literature.

General Procedure for Aminobenzo[*b*]thiophenes (1–11). To a mechanically stirred, cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzonitrile in 100 ml of DMF was added dropwise a solution containing 36 mmol of sodium sulfide (nonahydrate) in 20 ml of water. The mixture was stirred in the cold for 15 min and the alkylating agent (3 ml of chloroacetonitrile for **1–3** and **10**; 3 ml of chloroacetone for **4** and **5**; 36 mmol of phenacyl chloride for **6, 7,** and **11**; 36 mmol of chloroacetamide for **8** and **9**) was added dropwise or portionwise. The ice bath was removed and the mixture was stirred for an additional time (30 min for **1–5** and **10**; 1 hr for **6–9** and **11**). It was poured into ice water and the crude product was collected and crystallized from the appropriate solvent (Table I).

2-Chloro-6-[(2-cyanoethyl)thio]benzonitrile (12). A solution of 3 g of potassium hydroxide in 15 ml of water was added dropwise to a stirred, cold solution (ice bath) containing 5.5 g (30 mmol) of 2-chloro-6-nitrobenzonitrile and 3.1 g (36 mmol) of 3-mercaptopropionitrile[9] in 60 ml of DMF. The mixture was stirred in the cold for 10 min and then poured into ice water. The solid was collected and crystallized from alcohol to yield 2.7 g (40%) of product, mp 96–97°.

General Procedure for Aminobenzo[*b*]thiophenes 13–15. To a stirred, cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzonitrile and 3.1 g (36 mmol) of 3-mercaptopropionitrile[9] in 60 ml of DMF was added dropwise a solution of 5 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 15 min (30 min for preparation of **14**), and the alkylating agent (3 ml of chloroacetonitrile for **13** and **15**; 3.5 ml of chloroacetone for **14**) was added dropwise. After it had been stirred in the cold for an additional 2 hr, the mixture was poured into ice water. The crude product was collected and crystallized from the appropriate solvent (Table I).

Acknowledgment. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**1,** 52673-85-5; **2,** 52673-86-6; **3,** 52673-87-7; **4,** 52673-88-8; **5,** 52673-89-9; **6,** 52673-90-2; **7,** 52673-91-3; **8,** 52673-92-4; **9,** 52673-93-5; **10,** 52673-94-6; **11,** 52673-95-7; **12,** 52673-96-8; **13,** 34761-14-3; **14,** 22720-75-8; **15,** 52673-97-9; 2-chloro-6-nitrobenzonitrile, 6575-07-1; 4-chloro-2-nitrobenzonitrile, 34662-32-3; 2-chloro-5-nitrobenzonitrile, 16588-02-6; *o*-nitrobenzonitrile, 612-24-8; 2,6-dinitrobenzonitrile, 35213-00-4; 6-nitro-*o*-anisonitrile, 38469-85-1; sodium sulfide, 1313-82-2; chloroacetonitrile, 107-14-2; chloroacetone, 78-95-5; phenacyl chloride, 532-27-4; chloroacetamide, 79-07-2; 3-mercaptopropionitrile, 1001-58-7.

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A New Synthesis of $N^{\alpha},N^{G,G}$-Tribenzyloxycarbonyl-L-arginine and Related Derivatives

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Among the guanidino protected arginine derivatives[1] used in peptide synthesis, $N^{\alpha},N^{G,G}$-tribenzyloxycarbonylarginine (II)[2,3] has proven to be a useful intermediate for the addition of an arginine residue to the amino terminus of a synthetic peptide. The considerable difficulty with which II is prepared, however, has discouraged its use in peptide synthesis except in special cases, *e.g.,* the synthesis of L-arginyl-L-arginyl sequences.

We report herein a procedure for the preparation of II and closely related derivatives which is experimentally simple and which consistently provides product yields substantially greater than the procedure[2,3] heretofore used. The salient features of the procedure involve the use of an

alkyl pentachlorophenylcarbonate as the alkyloxycarbonyl donor and *N*-trimethylsilylacetamide to promote *in situ* silyl ester formation[4] and to scavenge pentachlorophenol produced in the alkyloxycarbonylation reaction. Work-up of the reaction mixture is simplified by the ready hydrolysis of silyl esters and ethers, the high solubility of lithium acetate in absolute ethanol, and the ready precipitation of the crystalline lithium salts of II and closely related derivatives from ethanolic lithium acetate solution without coprecipitation of lithium pentachlorophenoxide. Other derivatives that have been prepared by the procedure are N^{α}-*p*-methoxybenzyloxycarbonyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginine (IV),[5] N^{α}-benzoyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginine (VI), and $N^{\alpha},N^{G,G}$-tri-*p*-methoxybenzyloxycarbonyl-L-arginine (VIII). The latter two derivatives are new compounds, and their use in peptide synthesis will be reported elsewhere.

Experimental Section[6]

Lithium $N^{\alpha},N^{G,G}$-Tribenzyloxycarbonyl-L-arginate (I). To 210 ml of dry DMF were added 20.88 g (0.12 mol) of L-arginine and 160 g (0.4 mol) of benzyl pentachlorophenylcarbonate.[7] The resulting suspension was stirred and heated to 60°. *N*-Trimethylsilylacetamide (78.6 g; 0.6 mol) was added to the mixture and the mixture was stirred for 60 hr at 60°.

After addition of 20 ml of water to the reaction mixture the DMF was evaporated *in vacuo*. The resulting residue was dissolved in absolute ethanol and the solution was added to a hot saturated solution of 50 g of lithium acetate in ethanol. The resulting mixture was cooled slowly to room temperature and then maintained at 4° overnight. A precipitate formed and was filtered. The collected solid was triturated with hot ethyl acetate and then was recrystallized from a minimum volume of boiling methanol. The solid was recovered by filtration and dried *in vacuo* to obtain 39 g (56%) of the title compound, mp 153–155°. An analytical sample was recrystallized from a mixture of methanol and acetone, mp 156–157°; $[\alpha]^{24}D$ +10.6 (*c* 1.5, methanol).

Anal. Calcd for $C_{30}H_{31}N_4O_8Li$: C, 61.85; H, 5.36; N, 9.62; mol wt 582.52. Found: C, 61.75; H, 5.50; N, 9.34.

$N^{\alpha},N^{G,G}$-tribenzyloxycarbonyl-L-arginine (II). Lithium $N^{\alpha},N^{G,G}$-tribenzyloxycarbonyl-L-arginate (10.0 g; 0.017 mol) was suspended in ethyl acetate. The suspension was neutralized by addition of 2% aqueous sulfuric acid. The ethyl acetate layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting residue was recrystallized from ethyl acetate to afford, after drying *in vacuo*, 9.1 g (92%) of the title compound: mp 138–139°; $[\alpha]^{25}D$ +15.1 (*c*, 1.5, chloroform) (lit.[2] mp 138–139°; $[\alpha]^{25}D$ +15.5 (*c* 1.5, $CHCl_3$)).

Anal. Calcd for $C_{30}H_{32}N_4O_8$: C, 62.49; H, 5.59; N, 9.72; mol wt 576. Found: C, 62.21; H, 5.80; N, 9.43.

Lithium N^{α}-*p*-Methoxybenzyloxycarbonyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginate (III). The title compound was prepared from N^{α}-*p*-methoxybenzyloxycarbonyl-L-arginine[5] as described in the procedure for I, except that the reaction time was limited to 34 hr. III was obtained in 63% yield: mp 209–210°; $[\alpha]^{24}D$ +9.9 (*c* 1.5, methanol).

Anal. Calcd for $C_{31}H_{33}N_4O_9Li$: C, 60.78; H, 5.43; N, 9.15; mol wt 612.55. Found: C, 60.51; H, 5.67; N, 9.08.

N^{α}-*p*-Methoxybenzyloxycarbonyl-N^{G},N^{G}-dibenzyloxycarbonyl-L-arginine (IV). Neutralization of III with 0.75 *N* aqueous citric acid gave the title compound in 91% yield: mp 139–141°; $[\alpha]^{25}D$ +16.6 (*c* 1.5, chloroform) (lit.[5] mp 135–136°; $[\alpha]^{25}546$ +14.0° (*c* 1.5, EtOH)).

Anal. Calcd for $C_{31}H_{34}N_4O_9$: C, 61.38; H, 5.65; N, 9.24; mol wt 606.63. Found: C, 61.65; H, 5.88; N, 9.46.

Lithium N^{α}-Benzoyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginate (V). The title compound was prepared from N^{α}-benzoyl-L-arginine[8] as described in the procedure for I, except that the reaction time was limited to 48 hr. V was obtained in 50% yield: mp 207–209°; $[\alpha]^{25}D$ +28.3 (*c* 1.5, chloroform).

Anal. Calcd for $C_{29}H_{29}N_4O_7Li$: C, 63.03; H, 5.29; N, 10.14; mol wt 552.49. Found: C, 62.80; H, 5.13; N, 10.29.

N^{α}-Benzoyl-N^{G},N^{G}-dibenzyloxycarbonyl-L-arginine (VI). Neutralization of V with 0.75 *N* aqueous citric acid gave the title compound in 83% yield: mp 172–173°; $[\alpha]^{25}D$ +20.0 (*c* 1.5, DMF).

Anal. Calcd for $C_{29}H_{30}N_4O_7$: C, 63.73; H, 5.53; N, 10.25; mol wt 546.58. Found: C, 63.59; H, 5.25; N, 10.07.

Lithium $N^{\alpha},N^{G,G}$-Tri-*p*-methoxybenzyloxycarbonyl-L-arginate (VII). The title compound was prepared exactly as described in the procedure for I. VII was obtained in 50% yield: mp 146–148°; $[\alpha]^{25}D$ +17.5 (*c* 1.0, DMF).

Anal. Calcd for $C_{33}H_{37}N_4O_{11}Li$: C, 58.93; H, 5.55; N, 8.33; mol wt 672.60. Found: C, 58.70; H, 5.76; N, 8.54.

$N^{\alpha},N^{G,G}$-Tri-*p*-methoxybenzyloxycarbonyl-L-arginine (VIII). Neutralization of VII with 0.5 *N* sulfuric acid gave the title compound in 80% yield: mp 125–128°; $[\alpha]^{25}D$ +1.9 (*c* 1, DMF).

Anal. Calcd for $C_{33}H_{38}N_4O_{11}$: C, 59.45; H, 5.75; N, 8.40; O, 26.40; mol wt 666.68. Found: C, 59.15; H, 5.84, N, 8.45; O, 26.57.

Registry No.—I, 52748-08-0; II, 52795-86-5; III, 52748-09-1; IV, 52748-10-4; V, 52748-11-5; VI, 52748-12-6; VII, 52748-13-7; VIII, 52748-14-8; L-arginine, 74-79-3; benzyl pentachlorophenylcarbonate, 13795-28-3; *p*-methoxybenzyl pentachlorophenylcarbonate, 52795-87-6.

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Ethylene Iminocarbonate

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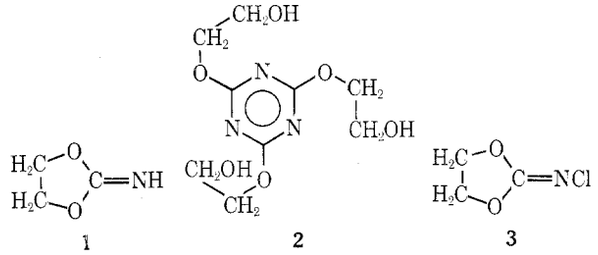
We wish to record here a preparation and characterization of ethylene iminocarbonate (**1**), and its spontaneous conversion to a trimer (**2**). Although the hydrochloride of **1** was described some time ago,[2] neither **1** itself nor **2** have apparently been reported previously.



1 **2** **3**

Ethylene chloriminocarbonate (**3**), easily available from ethylene glycol, potassium cyanide, and chlorine,[3] reacted with sodamide in liquid ammonia, slowly at −80°, vigorously at −50° to −60°. At the latter temperature, the reaction was complete in about 1 hr. Low-temperature work-up gave up to 25% yield of white crystals, mp 38–45° dec, assigned the structure of ethylene iminocarbonate based on spectral data. A by-product, white crystals of mp 117–120° (sintering), was isolated in 25–40% yield. From spectral evidence, it was assigned a trimer structure, most likely **2**.

After about 30 min at room temperature, the crystals of **1** started to melt and 2.5 hr after isolation, decomposition was extensive (effect of traces of base cannot be excluded). Upon further standing or trituration with acetonitrile, crystals of the trimer **2** were formed. On the other hand, the nmr spectrum of a solution of **1** in acetonitrile-d_3 remained unchanged for more than 2 weeks at room temperature.