Chemistry of Thienopyridines. XXVI. Synthesis of
6-(γ-Diethylaminopropylamino)thieno[2,3-b]pyridine (1)

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6-(γ-Diethylaminopropylamino)thieno[2,3-b]pyridine (3b) was obtained (58% yield) from copper-promoted aminodechlorination of 6-chlorothieno[2,3-b]pyridine at 168°. A mechanistic rationalization for the reaction and the mass spectral fragmentation pattern for 3b are presented.

In a previous paper (3) we reported the synthesis of three 4-(ω-dialkylaminoalkylamino)thieno[2,3-b]pyridines, including 1b, by the successive steps of: (a) heating 4-chlorothieno[2,3-b]pyridine 7-oxide (2a) with an excess of the corresponding dialkylaminoalkylamine at 100°; and (b) de-N-oxygenation of the intermediate compound (e.g. 2b). The presence of the N-oxide function served to

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a, x = Cl

c, x = n-BuNH-

e, x = Et₂N(CH₂)₃CHNH- / CH₃
     (e, x=Et₂N(CH₂)₃CHNH– under CH₃)

b, x=Et₂N(CH₂)₃NH-

d, x=(n-Bu)₂N(CH₂)₃NH-

facilitate nucleophilic displacement of the 4-chloro group by the free amine (4). We now report the synthesis of 3b, isomeric with 1b, by means of the copper-promoted nucleophilic substitution of the 6-chloro group in 3a, as well as qualitative experimental observations which relate to the mechanism of the reaction.

Compound 3b was obtained by heating 3a and a small amount of copper powder with excess γ-diethylaminopropylamine in a sealed tube at 168°; these are essentially the same conditions as described for the reaction between 2-chloroquinoline and n-butylamine (5). The product (3b) was isolated by molecular distillation (58% yield) and purified further by recrystallization of the dipicrate. Efforts to extend this copper-promoted (6) aminodehalogenation reaction (7) to the syntheses of the analogous N-substituted 4- and 6-aminothieno[2,3-b] pyridines 1c, 1e, and 3e were only partially successful, since we were unable to find suitable derivatives for the final step of purification. However, these four compounds were obtained as transparent, distilled resins which showed appropriate pmr and high resolution mass spectra. The pmr spectra of all of the distilled products clearly established that ipso-substitution (8) had occurred, and to the exclusion (within the accuracy of the measurement) of cine-substitution (9a,10). Moreover, the formation of 1e

(19% crude yield) from 1a by the copper-promoted reaction contrasts sharply with the observation that 2a and the corresponding amine (1-methyl-4-diethylaminobutylamine) do not react directly at 100° (11). It is readily apparent that cuprous chloride is formed from the copper promoter, inasmuch as the slightly yellow liquid product mixture becomes blue-green when the reaction tube is opened to air (12).

Scheme 1 (wherein TP refers to the thienopyridyl group) is proposed as a rational mechanistic sequence for the copper-promoted aminodechlorination, as based on the foregoing observations.

Scheme I (a)

Cu + TPCl → Cu⁺ + TPCl⁻̇	1
TPCl⁻̇ → TP· + Cl⁻	2
TP· + TPCl → TP⁺ + TPCl⁻̇	3
TP⁺ + RNH₂ → TPṄH₂R	4
TPṄH₂R + RNH₂ ⇌ TPNHR + RNH₃⁺	5

(a) Specifically, TPCl represents 1a or 3a, while R is an alkyl or dialkylaminoalkyl group in the present study.

Steps 1 and 2 of Scheme 1 are an adaptation of a proposal of Bacon and Stewart (13) for copper promotion by means of electron transfer to a halo compound (TPCl here). The unstable anion radical which results then dissociates into a thienopyridyl free radical and a chloride ion. These two steps are the same as those proposed by Kim and Bunnett (14) in the $S_{RN}1$ reaction of an amide ion with an aryl halide, except that the source of the electron transferred is clearly indicated in our scheme. Likewise, the TPCl molecule may be considered an electrophore (analogous to a halonitrobenzene) which accepts an electron into an unoccupied π^* orbital and, then, (following internal electronic rearrangement) ejects a chloride ion, in the manner proposed in electrochemical reductions (15,16). Since it is unlikely that amide ions are present in our reaction mixture, we propose, instead, that the free amine attacks the thienopyridyl cation (step 4), which results from electron transfer between the free radical TP· and another molecule of TPCl (step 3). It seems reasonable that a chlorothienopyridine should be more electron attracting

than a thienopyridyl radical. Step 5 is merely a proton-transfer reaction between amines of differing basicities. Altogether, steps 1-4 represent a chain reaction, wherein a copper atom serves to initiate the chain (step 1), steps 2 and 3 represent chain propagation, and step 4 provides chain termination. Either the thienopyridyl free radical (14) or the thienopyridyl cation (9b) should result in *ipso*-substitution. In fact, as evidenced by mass spectral fragmentation patterns (*vide infra*) a thienopyridyl cation, especially when the positive charge is localized at C-6, has considerable stability. An analog and precedent for step 4 is the attack of water on an aryl cation in the hydrolysis of a diazonium salt (9b).

Scheme 2 gives the mass spectral fragmentation pattern for amine **3b**. As with the previously reported **2b** (the *N*-oxide of the 4-isomer, **1b**) (17), bond fission occurs predominantly in the alkylamino side chain to produce prominent peaks at m/e 163 (**5**), 86 (most abundant), 72, and 58. The 6-thienopyridyl cation (**6**) is considerably more abundant (22%) than is the isomeric ion **7** (6%) from **2b**. In analogy to its isomer, **6** may arise from dissociation of **5**.
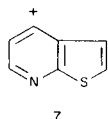
Scheme 2

Mass Spectral Fragmentation
Pattern for 3b (a)
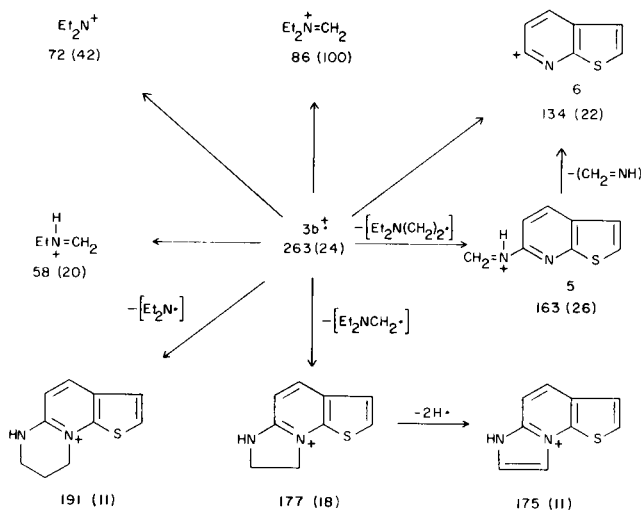
(a) Includes all peaks of relative abundance ≥ 10%, except for 42 (17), 56 (15), and 84 (16). Numbers in parentheses represent % relative abundances.

EXPERIMENTAL

General Procedure.

A mixture of 0.33-0.5 g. (1.9-3 millimoles) of 4- or 6-chlorothieno[2,3-*b*]pyridine (**1a** or **3a**) (19), 41-54 millimoles of liquid amine (variously *n*-butylamine, 3-diethylaminopropylamine, 3-di-*n*-butylaminopropylamine, and N^1,N^1-diethyl-1,4-pentanediamine — all commercially available), and ca. 0.1 g. (1.6 mg.-atoms) of copper powder ("Bendalin #100 gold bronze," George Benda, Boonton, New Jersey) was heated in a sealed carius tube at 168 ± 2° for 4.5 hours (5). When it had cooled to room temperature, the tube was opened (no pressure noted) and the contents (unreacted copper, sometimes a small amount of white solid — probably an amine salt, and a yellow liquid which turned light blue-green on exposure to air) were distilled at ca. 20 mm pressure in order to remove unreacted liquid amine and possible volatile byproducts. The residue was extracted with a mixture of water and chloroform. Evaporation of the dried (sodium sulfate) chloroform layer and evaporative distillation at 0.5 mm pressure and a temperature in the range of 165-200° gave a yellow viscous liquid or resin.

6-(γ-Diethylamino)propylaminothieno[2,3-*b*]pyridine (3b).

The distilled liquid was converted into its dipicrate (89% yield), obtained as yellow granules from absolute ethanol, m.p. 160-161°.

Anal. Calcd. for $C_{26}H_{27}N_9O_{14}S$: C, 43.3; H, 3.8; N, 17.5. Found: C, 43.0; H, 3.6; N, 17.7.

Purified **3b** was recovered by shaking the dipicrate with a mixture of 5% aqueous lithium hydroxide and dichloromethane and then evaporating the dried organic layer; ir (chloroform): 3420 cm⁻¹; pmr (deuteriochloroform): δ 7.69 (d, 1, J = 8.5 Hz, H-4), 7.01 (s, 2, H-2 and H-3), 6.36 (d, 1, H-5), 5.75 (broad s, 1, NH), 3.47 (t, 2, J = 6 Hz, CH_2N), 2.4-2.7 (m, 6, [CH₃CH_2]₂NCH_2), 1.76 (pentet, 2, J = 6 Hz, CH₂CH_2CH₂), 1.03 ppm (t, 6, J = 7 Hz, [CH_3CH₂]₂N); ms: (105°) [See Scheme 2]. Exact mass: Calcd. for $C_{14}H_{21}N_3S$: 263.146. Found: 263.146.

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