

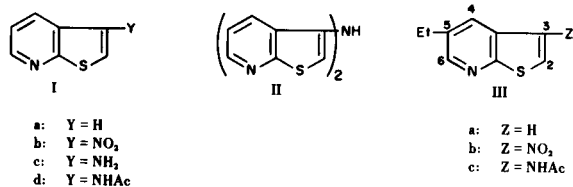
Chemistry of Thienopyridines. XVI. Direct Reductive Acetylation of 3-Nitro-5-ethylthieno[2,3-*b*]pyridine (1)

L. H. Klemm (2) and Henning Lund (3)

Department of Chemistry, University of Oregon, Eugene, Oregon 97403 (U.S.A.) and
Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

Received July 13, 1973

In a previous paper (4) it was noted that treatment of 3-nitrothieno[2,3-*b*]pyridine (Ib) with iron and glacial acetic acid at 100° gave (as the only isolated substance) a low yield of the condensation product bis-(3-thieno[2,3-*b*]pyridyl)amine (II), probably formed *via* Ic as an inter-



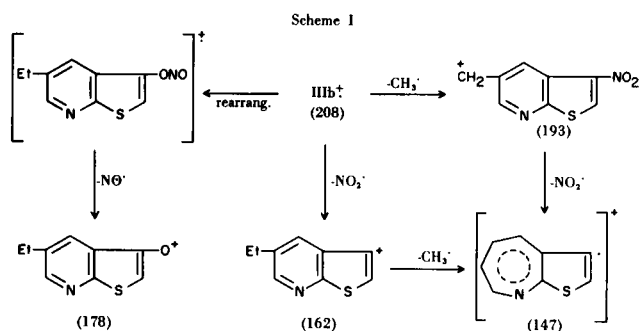
mediate. Although crystalline Ic could be obtained in fair yield by use of tin and hydrochloric acid as the reducing mixture, it was found that Ic has limited shelf stability. Like its unstable isostere 3-aminobenzo[*b*]thiophene (5), Ic can be stored as its stable acetyl derivative (Id), however. We wished to devise a method for reductive acetylation of nitrothienopyridines directly into their acetylamino derivatives without use of hydrochloric acid (which sometimes produces concurrent ring chlorination) (4).

As a model compound for study we synthesized 3-nitro-5-ethylthieno[2,3-*b*]pyridine (IIIb) by treatment of 5-ethylthieno[2,3-*b*]pyridine (IIIa) with mixed nitric-sulfuric acids, in the manner used to convert the parent compound Ia into Ib. It was then found that the simple expedient of adding acetic anhydride to the reducing mixture of iron and glacial acetic acid served to transform IIIb into IIIc in high yield (83%). Although we have not applied this procedure to other substrates, it could be useful, in general, for cases where the free amine is unstable or difficult to isolate (6).

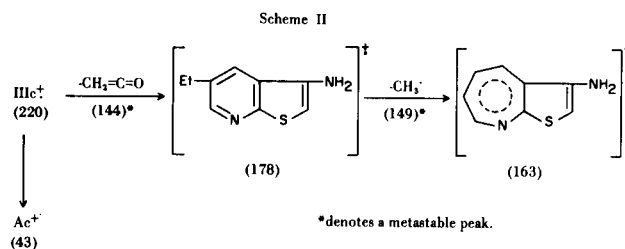
Structural assignment of the nitro group in IIIb to the 3-position was made on the basis of its pmr spectrum which showed a singlet for either H-2 or H-3 at δ 8.75 ppm plus a close doublet of doublets for H-4 and H-6 centered at 8.62. The large downfield shift ($\Delta\delta \approx 0.8$ ppm) from 7.79 for H-4 in IIIa (7) is consistent with location of the nitro group at C-3 in IIIb (and not at C-2). This assignment is corroborated by the fact that the signal

for H-4 is shifted upfield ($\Delta\delta \approx -0.7$ ppm) on conversion of IIIb into the amide IIIc.

Schemes I and II show some of the most important fragmentation pathways for IIIb and IIIc, respectively, in the mass spectrometer. For nitro compound IIIb loss of a methyl group from the molecular ion is the most likely transformation. Losses of NO (probably after rearrange-



ment of the nitro group) and NO₂ are also observed. The ion of *m/e* 147 is relatively abundant, perhaps because it can form *via* alternative pathways involving successive losses of methyl and NO₂ fragments in either order. Ions of *m/e* 193 and 147 may have the pyridylmethyl structure (as depicted for the former) or the rearranged azatropylium structure (shown for the latter) (8).



In contrast, amide IIIc undergoes initial loss of ketene (almost to the complete exclusion of loss of a methyl group) from the molecular ion. This step is followed by loss of methyl. Metastable peaks at 144 and 149 corroborate this sequence. The ion of *m/e* 178 is the most abundant one in the spectrum. Its proposed structure is

consistent with recent observations on the loss of ketene from acetanilides (9). The structure of the ion of *m/e* 163 is again uncertain.

EXPERIMENTAL (10)

5-Ethylthieno[2,3-*b*]pyridine (IIIa).

Compound IIIa was prepared by Wolff-Kishner reduction of 5-acetylthieno[2,3-*b*]pyridine (35 g.) (7) in the manner previously described, yield 57% of light yellow liquid, b.p. 118-120° (2 mm.).

3-Nitro-5-ethylthieno[2,3-*b*]pyridine (IIIb).

Following the procedure described for nitration of Ia (4), a solution of 38.6 g. of IIIa in 80 ml. of 98.5% sulfuric acid was treated with 35 ml. of 65% nitric acid. The cooled mixture was poured onto ice, and diluted to 1.8 liters with water. The cream-colored precipitate was collected by filtration, washed repeatedly with water until the filtrate was neutral, and dried in air, yield 26 g. (53%), m.p. 79-81°.

Further purification was effected by recrystallizations from 50° petroleum ether-benzene (4:1; filtration through celite) and absolute ethanol-cyclohexane (1:1) plus evaporative distillation at 90-110° (20 mm.) to give white needles, m.p. 85-86°; *uv* max (ethanol) 229 nm ($\log \epsilon$ 4.33), 251 (3.47), 318 (3.64); *ir* (chloroform) 1520, 1325-1340 cm^{-1} (nitro group); *pmr* δ 1.37 (t, 3, J_{Et} = 7.5 Hz, methyl group), 2.89 (q, 2, methylene group), 8.62 (d of d, 2, $J_{4,6}$ = 2 Hz, $\Delta\delta$ = 5.9 Hz, H-4 and H-6) (11), 8.75 ppm (s, 1, H-2); mass spectrum, *m/e* (relative abundance) 209 (31), 208 (95), 193 (100), 178 (23), 162 (30), 161 (25), 147 (82), 77 (38), 75 (25), 69 (31), 63 (22), 51 (22), 45 (25, HCS^+), 39 (34, C_3H_3^+).

Anal. Calcd. for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2\text{S}$: C, 51.9; H, 3.9; N, 13.5; S, 15.4. Found: C, 52.0; H, 3.9; N, 13.3; S, 15.4.

3-Acetylamino-5-ethylthieno[2,3-*b*]pyridine (IIIc).

A vigorously stirred mixture of 4 g. (0.019 mole) of nitro compound IIIb, 4.5 g. (0.08 g.-atom) of iron powder (reduced), 75 ml. of glacial acetic acid, and 10 ml. of acetic anhydride was heated to 120° momentarily, maintained at $100 \pm 5^\circ$ for 8 hours, and then left without heating for 16 hours. It was poured into ice-water and basified to pH 8 with sodium hydroxide. The emulsion which resulted from shaking this mixture with ether formed three phases (ether, water, and sludge) on standing overnight. The layers were separated and the latter two were extracted individually by swirling with fresh portions of ether several times until emulsification ceased. The sludge and aqueous layer were then recombined and extracted repeatedly by vigorous shaking with ether (12). Combined ether extracts were evaporated to leave as oily solid. Washing this product with a little ether and then repeatedly with water gave 3.5 g. (83%) of yellow prisms, m.p. 131-138°. Recrystallization from ethyl acetate gave colorless prisms, m.p. 139-140°; *uv* max (ethanol) 233 nm ($\log \epsilon$ 4.11, shoulders), 246 (4.25), 305 (3.30); *ir* (chloroform) 3270 (NH), 1665 and 1505-1525 cm^{-1} (amide bands); *ir* (potassium bromide): 3240, 1640, 1520 cm^{-1} ; *pmr* δ 1.15 (t, 3, J_{Et} = 7.5

Hz, methyl group), 2.21 (s, 3, Ac), 2.65 (q, 2, methylene group), 7.86 (s, 1, H-2), 7.94 (d, 1, $J_{4,6}$ = 2 Hz, H-4), 8.40 (d, 1, H-6), 9.15 ppm (broad s, 1, NH); mass spectrum *m/e* (relative abundance) 220 (93), 205 (4), 179 (25), 178 (100), 177 (24), 163 (85), 43 (31).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 60.0; H, 5.5; N, 12.7; S, 14.6. Found: C, 60.1; H, 5.7; N, 12.6; S, 14.6.

Acknowledgement.

One of us (L.H.K.) wishes to thank NATO headquarters, Bruxelles, Belgium for financial assistance in this research.

REFERENCES

- (1) For paper XV see L. H. Klemm, W. O. Johnson, and D. V. White, *J. Heterocyclic Chem.*, **9**, 843 (1972).
- (2) On leave from the University of Oregon, 1972-1973. Correspondence in regard to this paper should be directed to this author at the University of Oregon.
- (3) At the University of Aarhus, where this research was conducted.
- (4) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *J. Heterocyclic Chem.*, **7**, 373 (1970).
- (5) B. Iddon and R. M. Scrowston, "Advances in Heterocyclic Chemistry," A. R. Katritzky and A. J. Boulton, Eds., Vol. 11, Academic Press, New York, N. Y., 1970, pp. 283-285, 288.
- (6) Efforts to accomplish electrochemical reductive acetylation of Ib and IIIb to *N,O*-diacetylhydroxylamines by a procedure which works well for less sensitive compounds (unpublished results from the University of Aarhus) gave only tar and unidentified byproducts. Because of the metal-complexing properties of system Ia [cf. L. H. Klemm, J. Shabtai, and F. H. W. Lee, *J. Chromatog.*, **51**, 433 (1970)] catalytic reductive acetylation of IIIb was not attempted.
- (7) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *J. Org. Chem.*, **34**, 347 (1969).
- (8) Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y., 1971, pp. 378-384.
- (9) N. Uccella, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, **6**, 229 (1973) and references cited therein.
- (10) Elemental analyses were performed by Mikrokemisk Laboratorium, Ballerup, Denmark. Infrared spectra were obtained by means of a Perkin-Elmer Infracord; *pmr* spectra, by means of a Varian A-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal standard; ultraviolet spectra, by means of a Bausch and Lomb Spectronic 505 instrument; and mass spectra, by means of a CEC 21-104 or a Perkin-Elmer MS 270 instrument at 70 eV. Except for one small peak from IIIc only mass spectral peaks of relative abundance > 20% are reported.
- (11) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 89-90.
- (12) The glassware is conveniently cleaned by means of concentrated hydrochloric acid.