Syntheses of Two Thienopyridines by Thermolytic Cyclization Reactions (1)

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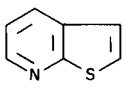
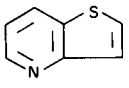
Sir:

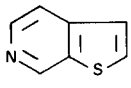
Thienopyridines are of pharmacological interest because of their isosterism with quinoline and isoquinoline. They are of theoretical interest since they combine into one fused aromatic system, the pyridine ring (normally susceptible to facile nucleophilic substitution) and the thiophene ring (normally susceptible to facile electrophilic substitution). Although four of the six possible isomeric thienopyridines have been reported in the literature (5-8), it is only recently that a satisfactory preparative method for any one of them has been devised. Thus, Klemm, *et al.* (9) obtained thieno[2,3-*b*]pyridine (I) by a three-step synthesis from thiophene (nitration, reduction to a thienylammonium salt, and condensation-cyclization with malondialdehyde tetraethyl acetal). Thieno[3,2-*b*]pyridine (II) is obtained as a by-product in the synthesis of I. We now wish to report preparative two-step syntheses of II and of thieno[2,3-*c*]pyridine (III) from 2- and 4-vinylpyridines, respectively.



I



II

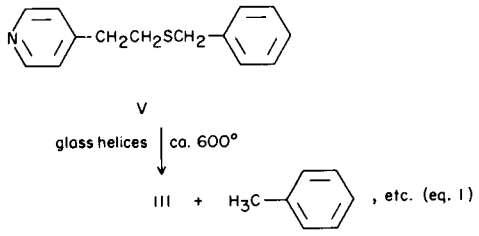


III

To an ice-cold, stirred solution made by treatment of 50 ml. of ethanol with 0.75 g. of sodium was added 35 g. of benzyl mercaptan and then (dropwise, over a period of 30 minutes) 30.2 g. of freshly distilled 2- or 4-vinylpyridine. Additional ethanol (30 ml.) was added and the solution was allowed to stand at room temperature for 2.5 hours. Evaporation of solvent gave 63 g. (98%) of crude benzyl 2-(2- or 4-pyridyl)ethyl sulfide as a crude liquid (IV or V, respectively), used without further purification. IV was identified by nmr spectrum and the formation of a picrate, m.p. 104.5-105.5°.

Anal. Calcd. for $C_{20}H_{18}N_4O_7S$: C, 52.39; H, 3.96; N, 12.22; S, 7.00. Found: C, 52.11; H, 3.93; N, 12.20; S, 6.60. Similarly, V (appropriate nmr spectrum) gave a picrate, m.p. 112.5-113°. Found: C, 52.63; H, 4.08; N, 12.37; S, 7.08.

Thermolytic cyclizations of IV and V (eq. 1) were



conducted in a flow apparatus which consisted of a vertically mounted Vycor tube (3 cm. i.d.), packed to a height of 45 cm. with 3/32-inch Pyrex glass helices throughout an isothermal zone (estimated variation in temperature ± 3°). Hydrogen sulfide or nitrogen was used as a carrier gas (flow rate *ca.* 10 liters/hour) and the neat liquid sulfide (50 g.) was added dropwise at a uniform rate to the top of the reaction tube over a period of 1.7 hours. An ether extract of the total product, obtained from acetone washings of the cooled helices plus the contents of an ice-cold receiver, was separated into basic and non-basic fractions by extraction with 10% hydrochloric acid.

Fractional distillation of the basic component from reaction of V at 605° (optimal temperature) gave III as a yellow liquid (58 mole % yield), b.p. 73-75° (0.5 mm.). This liquid was converted largely to crystals on cooling (m.p. 59-60° from hexane), and was identified by direct comparison (vpc retention volume, nmr spectrum, m.p. and m.m.p. of picrates) with an authentic sample prepared by the method of Herz and Tsai (6), m.p. 54-55°. Identified in the non-basic fraction were toluene, stilbene, and 2-phenylthianaphthene.

The crude basic fraction from reaction of IV at 600°

(optimal temperature) was found to contain 28% of II (27 mole % yield) by vpc analysis. Concentration of this fraction and chromatography by means of Alcoa F-20 alumina and benzene gave purified II, identical in vpc retention volume and nmr spectrum with an authentic sample prepared from 2-vinylpyridine and hydrogen sulfide (8).

It is presumed that the initial step in the thermal reaction involves homolytic splitting of the $C_6H_5CH_2$-S bond (estimated dissociation energy 51 kcal./mole), which is very likely the weakest bond in IV or V (*cf.* $PyCH_2CH_2$-S, est. 69; $PyCH_2$-CH_2S, est. < 63) (10). Cyclization and dehydrogenation of the resultant pyridylethylthiyl radical would then complete the reaction.

REFERENCES

(1) This investigation was supported by research grants No. CA-5969 from the National Cancer Institute and No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. This is paper V in the series on the Chemistry of Thienopyridines. For paper IV see L. H. Klemm and R. Zell, *J. Heterocyclic Chem.*, 5, 773 (1968).

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(9) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *ibid.*, 34, in press (1969).

(10) The bond dissociation energies are estimated from those reported for $C_6H_5CH_2$-SCH_3, C_2H_5-SC_2H_5, and $C_6H_5CH_2$-CH_3, respectively. See T. L. Cottrell, "The Strengths of Chemical Bonds", 2nd ed., Butterworths Scientific Publications, London, 1958.

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