Chemistry of Thienopyridines. VI. Reaction of Hydrogen Sulfide with Pyridines Bearing C_2-Groups in the 3-Position (1)

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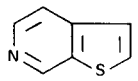
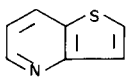
3-Substituted pyridines (bearing vinyl, ethyl, α-hydroxyethyl, and acetyl substituents) react with hydrogen sulfide at 630° to give low yields of thieno[2,3-*b*]pyridine and thieno[3,2-*c*]-pyridine. For 3-vinylpyridine as substrate, it is proposed that a free-radical process is involved in this synthesis.

Although Hansch and Carpenter (3) were unsuccessful in their attempt to convert 4-vinylpyridine into thieno-[2,3-*c*]pyridine (I) by reaction with hydrogen sulfide in a flow system packed with a modified alumina at a temperature of *ca.* 600°, this goal has since been achieved (in 1-7%



I



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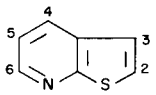
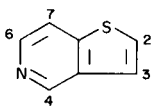


III



IV

yield) in our laboratory (4). Moreover, in analogous fashion, Klemm and Reed (5) were able to synthesize (in low yield) the isomeric thieno[3,2-*b*]pyridine (II) from 2-vinylpyridine. The procedure was modeled after that of Moore and Greensfelder (6) for conversion of styrene into benzo[*b*]thiophene (60% yield), a process which the authors described as catalyzed by the alumina packing. A rationale for these differences in yield was suggested by Klemm *et al.* (7) in terms of initial formation of $ArCH_2CH_2SH$ (where Ar is 4-pyridyl-, 2-pyridyl, or phenyl, respectively) and subsequent cyclization of this mercaptan during a requisite period of flatwise (π-type) adsorption of the aromatic ring onto the catalyst surface. Such adsorption should be favored for Ar = phenyl, but not for Ar = pyridyl, where edgewise or tilted (*n*-type) adsorption should predominate strongly. The experiments described in this paper were performed in an effort to check this hypothesis further and to search for possible new synthetic pathways to thieno[2,3-*b*]pyridine (III) and thieno[3,2-*c*]pyridine (IV).

For use in these studies 3-acetylpyridine (3-AcPy) was reduced catalytically to methyl 3-pyridyl carbinol (MPC, 83% yield) by a modification of the procedure of Strong and McElvain (8). Passing a mixture of MPC and *t*-butanol over alumina at 340° gave a mixture of 3-vinylpyridine (3-VPy, 56% yield) and 3-ethylpyridine (3-EtPy, 8% yield). The butanol (plus water obtained from it by dehydration) effectively maintains a lowered activity of the catalyst by displacing pyridine compounds from its surface. Thus, one obtains a considerably higher yield of 3-VPy (albeit contaminated with 3-EtPy) than has been reported by other methods (9), perhaps as a result of repression of polymer formation.

Data on the results of treating 3-VPy and allied compounds with hydrogen sulfide at 630° are presented in Table I. Examination of this table shows that a vinyl, an ethyl, an α-hydroxyethyl, or an acetyl group in the 3-position of the pyridine nucleus can be used (in the presence of hydrogen sulfide) as a source of the fused thiophene ring. The ethyl and the vinyl groups seem to be equivalent with regard to yields of thienopyridine products, while the hydroxyethyl and acetyl groups are less effective.

In consideration of the reducing-dehydrating conditions which prevail in the presence of alumina and hydrogen sulfide it seems likely that MPC and 3-AcPy are converted to 3-VPy and/or 3-EtPy as intermediates on the main route to III. In fact, relatively large amounts of these reduction-dehydration products are isolated in run 2. On the other hand, total formation of IV cannot be rationalized by the same pathway since the ratio of III:IV should

TABLE I

Reaction of 3-Substituted Pyridines with Hydrogen Sulfide at 630° (a)

Run No.	Starting Material Compound	Weight (g.)	Percentage Yields (b)					
			3-MePy	3-EtPy	3-VPy	III	IV	Other
1	3-VPy 3-EtPy	32.7 3.3	11	16	15	5.9	0.9	
2	MPC	40.5	10	42	22	2.2	0.9	(c)
3	3-AcPy	40	11	14	9	1.1	0.9	(d)
			2,5-DiMePy	2-Me-5-EtPy	2-Me-5-VPy	6-Me-III	6-Me-IV	
4	2-Me-5-VPy	50	8	18	0	2.2	0.3	(e)
5 (f)	2-Me-5-EtPy	40	8	53	6	2.4	0.3	(e)
6 (g)	2-Me-5-VPy	50	2	16	66	1.9	0.3	(h)

(a) Except in run no. 6, the tube was packed with chromia-alumina (Harshaw Chem. Co., Cr-0101 T, 1/8″ pellets). Otherwise, reaction conditions are identical for all runs. Data for runs 4 and 5 are reported, in part, in another article (10). Me denotes a methyl group. (b) Based on starting material used. (c) Also 3% yield of 3-AcPy. (d) Plus 25% recovery of 3-AcPy. (e) Plus 0.3-0.5% of III and 0.1-0.2% of IV. (f) Compare 4-Me-3-EtPy (starting material) which gives a 1% yield of 4-Me-III (10). (g) Tube packed with pyrex glass helices, 3/32″ i.d. (h) Also 0.1% yield of III.

then remain constant in runs 1-3. Although no MPC was identified in any reaction product mixture, 25% of the 3-AcPy used in run 3 was recovered.

It is apparent that reaction of 3-VPy (like its 2- and 4-isomers) with hydrogen sulfide gives only a low yield of thienopyridine product. On a preparative scale then, the recently described simple route to III (thiophene → 2-nitrothiophene → 2 thienylammonium salt → III) (35% overall yield), wherein condensation with malondialdehyde tetraethyl acetal comprises the last step (10), is much to be preferred. However, despite the low yield, reaction of 3-AcPy (or perhaps 3-EtPy) with hydrogen sulfide would seem to be the most convenient available synthetic route to IV (11). Rather than cyclization, the chromia-alumina packing seems to foster mainly polymerization of the vinylpyridine, reduction of the vinyl group, and cracking of the C_2-chain (4). Such undesired processes are probably enhanced through strong adsorption of the substrate molecules onto the chromia-alumina packing (*cf.* recovery of 2-Me-5-VPy from chromia-alumina in run 4 with that from glass helices in run 6). The close similarities of yields of 6-Me-IV in runs 4 and 6 point to the likelihood that adsorption and catalysis are unnecessary (indeed, are deleterious) to thienopyridine formation. Alternatively, we suggest that the conversion 3-VPy → III and IV may involve a non-catalyzed, thermal process whereby free-radical substitution into the pyridine ring occurs predominantly at the α-position and less readily at the γ-position, in accordance with known differences in susceptibilities to free-radical attack at these positions (12).

EXPERIMENTAL

Methyl 3-Pyridyl Carbinol.

A mixture of 125 g. (1.03 moles) of 3-acetylpyridine (Aldrich Chemical Co.), 100 ml. of 95% ethanol, and 0.7 g. of Adams' platinum oxide catalyst (Engelhard Industries) was shaken with hydrogen gas at 2-4 atmospheres pressure until 1.24 moles of hydrogen was absorbed. Filtration and evaporation of the reaction mixture gave a residue which was distilled at 0.25 mm., yield 105 g. (83%) of colorless liquid, b.p. 80-86°; lit. (8) 85% yield, b.p. 123-125° (5 mm.).

3-Vinylpyridine.

To the top of a vertically mounted tube (Monel, 2.6 cm. i.d.), packed to a height of 24 cm. with Harshaw alumina Al-0104 catalyst (1/8″ pellets, 99% Al_2O_3, activated for 2 hours at 340° in a flow of nitrogen gas) and maintained at 340° was added (60 drops/minute) a mixture of 188 g. of methyl 3-pyridyl carbinol and 88.5 g. of *t*-butanol (while a slow stream of nitrogen was continued). The effluent (collected in cold traps and con-

sisting of 63% yield of 3-VPy by nmr analysis) was separated from unreacted carbinol by distillation at 20 mm. pressure. The fraction boiling at 65-70° was collected as product and stored at 10° with a small amount of phenyl 2-naphthyl amine as inhibitor. It was redistilled prior to use and analyzed by nmr to ascertain the yields (typically 56% and 8%, respectively) of 3-VPy and 3-EtPy present. This mixture was used directly for reaction with hydrogen sulfide.

The nmr spectrum (determined in carbon tetrachloride by means of a Varian Associates 60 MHz instrument) of 3-VPy (freed from 3-EtPy by careful fractional distillation) showed these characteristics: δ_2 8.56, δ_4 7.66, δ_5 7.17, δ_6 8.43, $\delta_{\text{vinyl CH}}$ 6.67, $\delta_{\text{vinyl CH}_2}$ 5.75 and 5.29 ppm; $J_{2,5}$ = 2.2, $J_{5,6}$ = 4.6, $J_{4,6}$ = 1.9, $J_{4,5}$ = 8.0, J_{CH_2} = 1.1, J_{trans} = 18, J_{cis} = 11 Hz.

Reactions with Hydrogen Sulfide.

The apparatus (with either a pyrex tube or the aforementioned Monel tube), the general procedure, and product analysis (by nmr and vpc) were described elsewhere (10). In runs 1-3 the crude product was distilled at 70-80° (1.5 mm.) and then chromatographed on Alcoa F-20 alumina. Initial elution with cyclohexane gave III, identical in nmr spectrum with an authentic sample prepared from thiophene (10). Admixture of picrates of III (m.p. 179.5-181° for each) from the two sources showed no melting point depression.

Further elution of the chromatographic column with chloroform-benzene gave IV, identical in nmr spectrum with an authentic sample prepared by the method of Herz and Tsai (13,14). A picrate of the chromatographed sample formed bright yellow needles from ethanol, m.p. 226-227° (dec.); lit. (13) m.p. 224.5°.

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