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THE NEW SYNTHESIS OF 3-ALKOXYPYRIDINES

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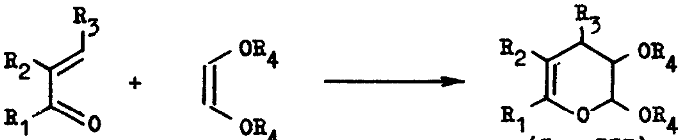
1,2-Dialkoxyethylenes add to α,β-unsaturated carbonyl compounds to give 2,3-dialkoxy-3,4-dihydro-1,2-pyrans:

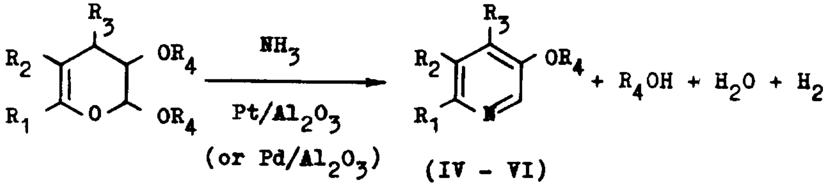


(I - III)

I - R_1, R_2 and R_3 = H, R_4 = C_2H_5 ;
II - R_1, R_2 and R_3 = H, R_4 = C_3H_7 ;
III - R_1 and R_2 = H, R_3 = CH_3, R_4= C_2H_5

The addition was carried out following the usual diene synthesis procedure (1, 2): heating of the combined reagents in the presence of inhibitors of polymerisation in sealed pressure vessels at temperatures above 120°.

It has now been found that 2,3-dialkoxy-3,4-dihydro-1,2-pyrans passed with an excess of ammonia at temperatures of 180-300° yield 3-alkoxypyridines according to the following equation:



(IV - VI)

IV - R_1, R_2 and R_3 = H, R_4 = C_2H_5 ;

V - R_1, R_2 and R_3 = H, R_4 = C_3H_7 ;

VI - R_1 and R_2 = H, R_3 = CH_3, R_4 = C_2H_5

This appears to be the first total synthesis of simple 3-alkoxypyridines.

The recorded syntheses of 3-alkoxypyridines make use of the reaction of 3-bromopyridine with sodium or potassium alkoholates (3) as well as treatment of potassium or sodium salts of 3-hydroxypyridine with alkyl halides (4).

The method reported here affords a fairly simple and universal synthesis of non-substituted as well as less accessible alkyl- and arylsubstituted 3-alkoxypyridines.

The results now obtained indicate that transformation of the 2,3-dialkoxy-3,4-dihydro-1,2-pyran structure to pyridine occurs by dehydrogenation and not by complete dealkoholation although the latter seemed more favourable in advance.

2,3-Diethoxy-3,4-dihydro-1,2-pyran (I) when saponified in acid medium and added to hydroxylamine according to (1) gave pyridine N-oxide in small yield. Our attempts, however, to transform 2,3-dialkoxy-3,4-dihydro-1,2-pyrans into pyridine derivatives when passing with ammonia over alumina (without Pt or Pd) were unsuccessful.

Acroleine and 1,2-diethoxyethylene in the equimolar ratio were heated in the presence of hydroquinone (1 % by weight) in sealed glass tubes during 10 hours at 180° to yield 74 % of 2,3-diethoxy-3,4-dihydro-1,2-pyran (I), b.p.$_{16}$ 82-83°, n_D^{20}1.4445, d_4^{20}1.0005. Found: C, 62.99, 62.82; H, 9.27, 9.62. $C_9H_{16}O_3$ requires: C, 62.77; H, 9.36%. The compound (I) was passed over a catalyst Pt/Al_2O_3 (0.5% Pt) at a rate of 0.05 g./min. per 1 ml. of catalyst in an ammonia and water steam current at 220°. From the catalysate 67% of 3-ethoxypyridine (IV) was isolated, b.p.$_{12}$ 77-78°, n_D^{20}1.5070, d_4^{20}1.0431, picrate m.p. 126.5-127.5°(corr.). Found: N, 15.86, 15.73. $C_{13}H_{12}N_4O_8$ requires: N, 15.90 %. Lit. (3) b.p.$_{15}$78-80°.

3-Ethoxypyridine thus obtained was identified by comparison with an authentic sample prepared according to (4) (no depression of a mixed melting point of the picrates, identity of the IR-spectra). The copper chloride paper chromatography (5,6) of 3-ethoxypyridine and other 3-alkoxypyridines obtained gave blue zones characteristic of 3- and 4-substituted pyridines.

Similarly, from acrolein and 1,2-di-n.propoxyethylene, 2,3-di-n.propoxy-3,4-dihydro-1,2-pyran (II) was prepared in 44% yield, b.p.$_{15}$ 104-105°, n_D^{20}1.4415, d_4^{20}0.9559. Found : C, 65.98, 65.76; H, 10.16, 10.17. $C_{11}H_{20}O_3$ requires: C, 65.98; H, 10.07 %. (II) at 250° over the same catalyst yielded 58.5% of 3-n.propoxypyridine (V), b.p.$_{11.5}$ 91-92°, n_D^{20}1.5015, d_4^{20}0.9987, picrate m.p. 103-104°(corr.). Found : N, 15.27, 15.14. $C_{14}H_{14}N_4O_8$ requires: N, 15.28%. Lit. (4) b.p.$_{15}$95-96°.

In the same manner, crotonaldehyde and 1,2-diethoxyethylene yielded 33% of 2,3-diethoxy-4-methyl-3,4-dihydro-1,2-pyran (III), b.p.$_{10}$ 80–82°, n_D^{20}1.4400, d_4^{20}0.9686. Found: C, 64.27, 64.25; H, 9.78, 9.87. $C_{10}H_{18}O_3$ requires: C, 64.48; H, 9.74 %. 2.0 g. (0.01 mole) of (III) and 6 ml. of water were passed in the vapour phase over 10 ml. of a catalyst Pt/Al_2O_3 with a 10-fold excess of ammonia during 45 min. to yield 1.05 g. (71.5%) of 3-ethoxy-4-methylpyridine, b.p.$_{11.5}$ 87–88°, n_D^{20}1.5054, d_4^{20}1.0082, picrate m.p. 141.5 – 142.3°(corr.). Found: N, 15.31, 15.16. $C_{14}H_{14}N_4O_8$ requires: N, 15.28 %.

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