Equilibrium between 4-Acetoxypyridine and *N*-Acetyl-4-pyridone; a Correction of the Literature

By **Ian Fleming** * and **D. Philippides**, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

The known compound, reported in the literature to be 4-acetoxypyridine, is shown to be *N*-acetyl-4-pyridone. In solution the two isomers are in equilibrium. 4-Pyridone is acetylated by acetic anhydride more rapidly and more completely than is 2-pyridone.

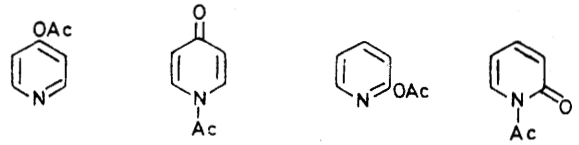
ACETYLATION of 4-pyridone has been described as yielding 4-acetoxypyridine (I),[1] a structure which appears not to have been questioned.[2,3] We needed this compound for comparison purposes, and have repeated the original preparation.[1] We have improved upon it by adding an excess of pyridine to the mixture of 4-pyridone and acetic anhydride. We have learned,[4] moreover, that use of the thallium salt of 4-pyridone also leads to a cleaner product than that obtained in the original recipe. The product obtained by any of these methods is, as the original claim maintains, crystalline and its m.p. varies with the method of preparation, presumably because of contamination with unchanged 4-pyridone, but which is usually 125—135°.

Both 2-acetoxypyridine and 3-acetoxypyridine are liquids; hence the high m.p. of '4-acetoxypyridine' was suspicious. Also, the i.r. spectrum of the crystalline material, prepared by the original [1] or by either of the improved methods, has a band at 1725 cm^{-1} (KBr), which further supported an alternative structure, *N*-acetyl-4-pyridone (II). We report here evidence which confirms that the compound long known as 4-acetoxypyridine is, in the solid state, *N*-acetyl-4-pyridone, and that in solution the two tautomers (I) and (II) are in equilibrium.

A fresh solution of the crystalline material in methylene

[1] F. Arndt and A. Kalischek, *Ber.*, 1930, **63**, 587.
[2] H. Meislich in 'Chemistry of Heterocyclic Compounds, Pyridine and its Derivatives,' ed. E. Klingsberg, Interscience, New York, 1962, Part 3, pp. 645 and 677.
[3] Except for a 3,5-di-iodo derivative, M. Dohrn and P. Diedrich, *Annalen*, 1932, **494**, 284.
[4] A. McKillop, personal communication.

dichloride had an i.r. band at 1750 cm^{-1} but within a few minutes a second band at 1775 cm^{-1} appeared. The latter, a value readily accommodated by the structure (I), is that expected for an aryl acetate. The n.m.r. spectrum of a fresh solution of the crystalline material in methylene dichloride showed a sharp singlet at τ 7·45 (3H) and an A_2B_2 system with the doublets (J 8 Hz) centred at τ 1·90 and τ 3·75. After a few minutes a second singlet appeared at τ 7·71 and also a second A_2B_2 system with broader doublets (J 6 Hz) at τ 1·45 and τ 2·92.



(I) (II) (III) (IV)

From many analogies, we would expect the 2-H signal of (I) to be at lowest field and the 3-H signal of (II) to be at highest field. We would also expect the 3-H signal of (I) to be at higher field than the 2-H signal of (II). This is in excellent accord with the assignment of the structure (II) to the isomer present in the fresh solution. Furthermore, both the higher coupling constant for (II) and the more obvious fine structure in the spectrum of (I) are consistent with this assignment. Finally, in their work on *N*-acetyl-2-pyridone (IV), McKillop and his co-workers [5] observed the peak due to the acetyl group to be 0·47 p.p.m. downfield from the corresponding signal in the spectrum of 2-acetoxypyridine (III). The peaks due to the acetyl groups of (I) and (II) are in the same order.

At equilibrium at room temperature in methylene dichloride, (I) and (II) are present in comparable quantities: in the ratio *ca.* 47 : 53. This contrasts with the equilibrium between 2-acetoxypyridine (III) and *N*-acetyl-2-pyridone (IV) where the *N*-acetyl tautomer is present only to the extent of *ca.* 10%.[5]

We have also examined the equilibria (1) and (2) in methylene dichloride, in each case from both directions. The equilibrium constants at 20° were 115 ± 15 for (1) and 4 ± 2 for (2).

$$\text{4-pyridone} + Ac_2O \underset{}{\overset{K = 115 \pm 15}{\rightleftharpoons}} [(I) + (II)] + AcOH \quad (1)$$

$$\text{2-pyridone} + Ac_2O \underset{}{\overset{K = 4 \pm 2}{\rightleftharpoons}} [(III) + (IV)] + AcOH \quad (2)$$

Under these conditions, *i.e.* with acetic acid present, the equilibrium mixture contains *ca.* 40% of (I) and 60% of (II). When equilibrium (1) was set up starting from the left, the *N*-acetyl tautomer (II) was formed more rapidly than the *O*-acetyl tautomer (I). 4-Pyridone is, therefore, more nucleophilic at the nitrogen than at the oxygen atom towards acetic anhydride. This contrasts with the case of phenanthridone, which is more nucleophilic at the oxygen atom towards benzoyl chloride.[6] Equilibrium (1), when it was approached from the left, was attained within an hour or so; most of which time was spent in (I) and (II) equilibrating with each other, the formation of the non-equilibrium mixture of (I) and (II) having taken place within a few minutes. In contrast, equilibrium (2), when it was approached from the left, took two or three weeks to be set up, and there was no substantial build-up above the equilibrium proportion of either tautomer (III) or (IV). The fact that the *N*-acetyl compound (II) is formed more rapidly than the *O*-acetyl compound (I) in the acetylation of 4-pyridone indicates that the enhanced production of the *N*-acetyl compound (IV) from the use of the thallium salt of 2-pyridone [5] may be due to the low temperature (and hence the non-equilibrium conditions) which can be used with this method, rather than to a specific effect of thallium(I) ions.

4-Pyridyl benzoate, which is also well known,[7] was prepared. In solution in methylene dichloride it appeared to exist entirely as the one tautomer, and is correctly formulated in the literature.

By the use of preparative methods similar to those used for the corresponding pyridone derivatives, we have also examined the previously unknown acetyl derivatives of carbostyril (2-quinolone) and 4-quinolone. Both gave crystalline products. In both cases, the *O*-acetyl tautomer appeared to be the only species present.

EXPERIMENTAL

N-Acetyl-4-pyridone.—4-Pyridone was acetylated by the literature method.[1] The following procedure appeared to be an improvement. 4-Pyridone (0·05 g, anhydrous) was dissolved in warmed acetic anhydride (0·05 ml) and pyridine (4 ml). After 4 h at room temperature the crystalline precipitate (65 mg, 89%) was filtered off in a dry box and washed with a little dry benzene. Attempts at further purification generally led to products contaminated with 4-pyridone. This product had the same i.r. spectrum as material prepared by the earlier method and by the thallium salt method.[4]

2-Acetoxyquinoline.—The sodium salt of carbostyril (1 g) was prepared with aqueous sodium hydroxide solution (6·9 ml; 1N); after 4 h the crystals were separated and dried (P_2O_5) *in vacuo*. Acetyl chloride (0·47 g) was added dropwise to the salt (1 g) and the reaction was completed by warming to 70°. The acetyl compound was extracted with boiling light petroleum (b.p. 30—40°). Evaporation of this solvent and any excess of acetyl chloride gave a solid residue, the spectroscopic properties of which indicated that it was *2-acetoxyquinoline*: $\nu_{max.}$ (KBr) 1770s, 1660s, and 1505m cm^{-1}, τ(CH_2Cl_2; fresh or

[5] A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Letters*, 1968, 4945.

[6] D. Y. Curtin and J. H. Engelman, *Tetrahedron Letters*, 1968, 3911.

[7] C. J. Cavallito and T. H. Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1166.

old solution) AB system at 1·75 and 2·83 (J 8 Hz), 1·9—2·6 (4H, m), and 7·64 (3H, s).* Recrystallisation of this material tended to increase the amount of carbostyril present.

4-*Acetoxyquinoline*.—4-Quinolone (0·5 g, sublimed) was heated to 100° in acetic anhydride (4 ml). The solution was kept at room temperature for 5 h and the excess of anhydride was removed *in vacuo* to leave a solid residue, the spectroscopic properties of which indicated that it was 4-acetoxyquinoline: $\nu_{max.}$ (KBr) 1760s, 1630m, and 1600 cm^{-1}, τ (CH_2Cl_2; fresh or old solution) AB system at 1·08 and 2·70 (J 5 Hz), 1·7—2·5 (4H, m), and 7·52 (3H, s). Attempted purification tended to increase the amount of 4-quinolone present.

3-*Acetoxyquinoline*.—For purposes not connected with this work, we also prepared 3-acetoxyquinoline, the details of which are given here. 3-Hydroxyquinoline [8] was acetylated in pyridine with acetic anhydride in the usual way to give 3-*acetoxyquinoline*, needles, m.p. 37·5° [from light petroleum (b.p. 30—40°)] (Found: N, 7·50. $C_{11}H_9NO_2$ requires N, 7·50%), $\nu_{max.}$ (Nujol) 1760s and 1600w cm^{-1}, τ(CH_2Cl_2) 7·63 (Ac).

[0/814 *Received, May 18th*, 1970]

* On one occasion a different spectrum was obtained from a crystalline sample. This spectrum showed a single acetyl peak at τ 7·36. In all the other spectra of 2-acetoxyquinoline which we recorded there is a small peak in this position. It seems likely that on that one occasion the *N*-acetyl tautomer had crystallised but that at equilibrium it is usually present in only very minor amounts.

[8] W. H. Mills and W. H. Watson, *J. Chem. Soc.*, 1910, 741.