Tetrahedron Letters No.48, pp. 4945-4948, 1968. Pergamon Press. Printed in Great Britain.

ACETYLATION OF THE THALLIUM(I) SALT OF 2(1H)-PYRIDONE. FORMATION OF N-ACETYL-2-(1H)-PYRIDONE.[1,2]

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(Received in UK 22 August 1968; accepted for publication 27 August 1968)

Curtin and Engelmann recently reported that treatment of the sodium salt of 6(5H)-phenanthridinone with benzoyl chloride at -20° led to almost exclusive formation of the kinetically controlled O-benzoyl derivative.[3] The authors also commented on (a) the paucity of data available on pairs of isomeric N- and O-acyl derivatives of simple heterocyclic systems; (b) the fact that N-acetylation of 2(1H)-pyridone had not yet been observed; and (c) that "N-acyl isomers of simple heterocyclic systems may be rather more accessible than is implied by their almost complete absence from the literature". In the present communication we present spectroscopic evidence in support of the hitherto unobserved N-acetyl-2(1H)-pyridone.[4] Acetylation of the thallium(I) salt[5] of 2(1H)-pyridone results in formation of both the N- and O-acetyl derivatives. At -40°, the N-acetyl derivative is present in the reaction product to the extent of about 40%; warming the reaction mixture from -40° to room temperature results in rearrangement of most (but not all) of the N-isomer to the O-isomer.

Acetylation at Room Temperature. Acetylation of the thallium(I) salt of 2(1H)-pyridone at room temperature in ether suspension[6] gave a product whose infrared spectrum showed, in addition to the carbonyl stretching band of 2-acetoxypyridine (1) at 1730-1760 cm^{-1}, medium intensity absorption at 1650-1675 cm^{-1}. This absorption was still present after distillation (bp 114°/15 mm), although the intensity was reduced. The nmr spectrum of the distillate (Figure 1) showed two distinct methyl singlets at δ 2.29 and 2.76, of relative intensity 10:1, the peak at δ 2.29 being due to the methyl group of 2-acetoxypyridine.[7] It was found by addition of the pure reagents that the singlet at δ 2.76 did not arise from acetyl chloride, acetic acid or acetic anhydride, whose methyl groups appear as singlets at δ 2.61, 2.05 and 2.13 respectively. The spectrum of the mixture of acetylated products also showed weak absorption in the region δ 6.0-6.7 characteristic of N-substituted-2-(1H)-pyridones.[8] The infrared absorption at 1650-1675 cm^{-1}, and the nmr signals at

δ 2.76 and δ 6.0-67, were therefore tentatively interpreted as evidence for the presence of ca. 10% of N-acetyl-2(1H)-pyridone (2) in the acetylation mixture.

Acetylation at -40°. Acetylation of the thallium(I) salt of 2(1H)-pyridone in ether suspension at -40°,[6] filtration of the reaction mixture, and determination of the nmr spectrum at -47° revealed the nuclear protons H_3 and H_5 of N-acetyl-2(1H)-pyridone much more clearly (Figure 2). When the sample was allowed to warm to room temperature and the spectrum recorded again, the intensity of the nuclear protons H_3 and H_5 was much reduced (Figure 3), in agreement with the expected N- to O-acetyl migration.

Chemical evidence for the N-acetyl group was obtained by addition of two drops of ethanol to a deuterochloroform solution of (1) and (2) (10:1 ratio), which led to rapid collapse of the methyl signal due to the N-acetyl group. As this signal disappeared, a new methyl singlet appeared at δ 1.98, due to ethyl acetate (confirmed by addition of ethyl acetate to the sample).[9]

Finally, acetylation at -40° in chloroform gave a mixture of products, the 100MHz nmr spectrum of which at -40° showed three methyl singlets at δ 2.05, 2.36 and 2.76 (Figure 4). The singlet at δ 2.05 was shown to be due to ethyl acetate (formed from the small amount of ethanol present in the solvent), while the singlets at δ 2.36 and 2.76 (relative intensitives 3:2) are assigned to the O- (1) and N-acetyl (2) derivatives respectively. As above, addition of ethanol to the spectroscopic sample resulted in rapid collapse of the N-acetyl singlet at δ 2.76 and reinforcement of the singlet due to ethyl acetate.[10]

To date, all attempts to isolate N-acetyl-2(1H)-pyridone have been unsuccessful, but further research on this and related compounds is in progress.

References

1. Thallium in Organic Synthesis. VII. Part VI : A. McKillop, D. Bromley and E. C. Taylor, J. Org. Chem., in press.

2. We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

3. D. Y. Curtin and J. H. Engelmann, Tetrahedron Letters, 3911 (1968).

4. Acylation of 2(1H)-pyridone has long been assumed to lead only to the O-acyl derivative. Treatment of the sodium salt of 2(1H)-pyridone with aroyl chlorides has been reported to give a mixture of products, the infrared spectrum of which was tentatively interpreted on the basis that both O- and N-acyl derivatives had been formed. (D. Y. Curtin and L. L. Miller, J. Amer. Chem. Soc., 89, 637 (1967), footnote 23).

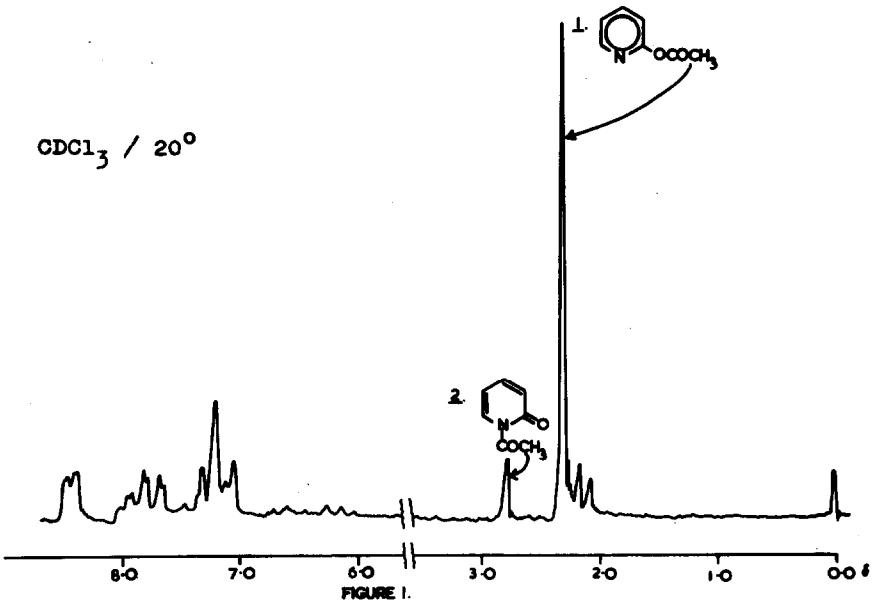

FIGURE 1.

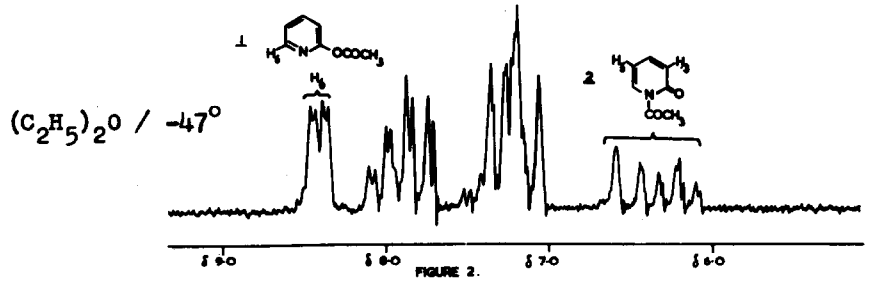

FIGURE 2.

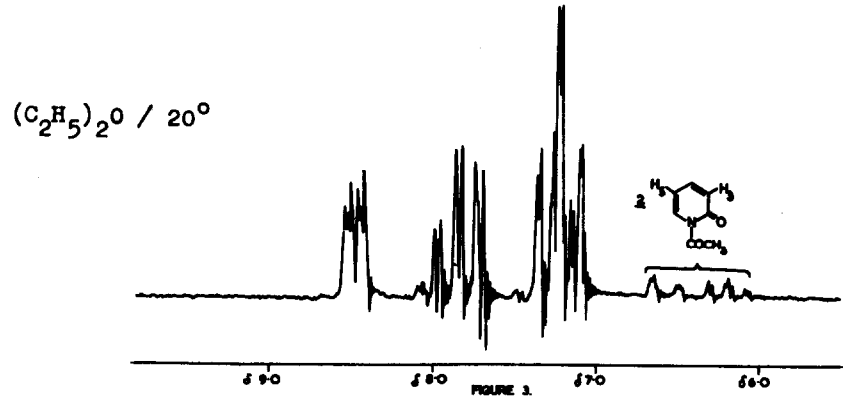

FIGURE 3.

nmr spectra at 60MHz (TMS as internal standard). Solvent and temperature as shown

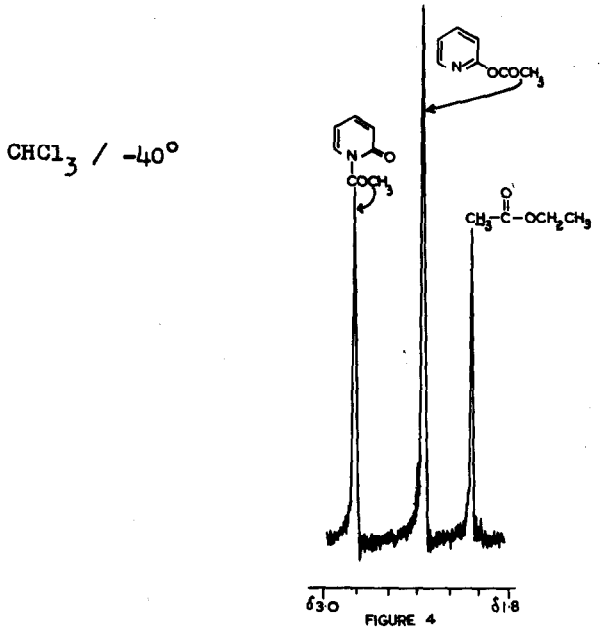

FIGURE 4

nmr spectrum at 100MHz (TMS as internal standard). Solvent and temperature as shown

5. Prepared in quantitative yield by addition of thallium(I) ethoxide to a solution of 2(1H)-pyridone in ethanol/pentane. Recrystallised from dimethylformamide; mp 155°.
6. Acetylations were performed by dropwise addition of the calculated amount of pure acetyl chloride to a stirred suspension of the thallium salt in the appropriate solvent. The precipitated thallium(I) chloride was removed by filtration.
7. B. Weinstein and D. N. Brattesani, J. Org. Chem., 32, 4107 (1967).
8. J. A. Elvidge and L. M. Jackman, J. Chem. Soc., 859 (1961).
9. The signal due to N-acetyl-2(1H)-pyridone (1) collapses rapidly, whereas that due to 2-acetoxypyridine (2) disappears only very slowly. The former compound (1) is thus an extremely active acetylating agent.
10. Addition of ethanol results not only in the disappearance of the signal due to N-acetyl-2(1H)-pyridone, but also in the precipitation of 2(1H)-pyridone from the sample. Consequently, the sample was filtered free of 2(1H)-pyridone before the spectrum was redetermined.