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Short Communications

The Reaction between Acetic Formic Anhydride and Salicylamide

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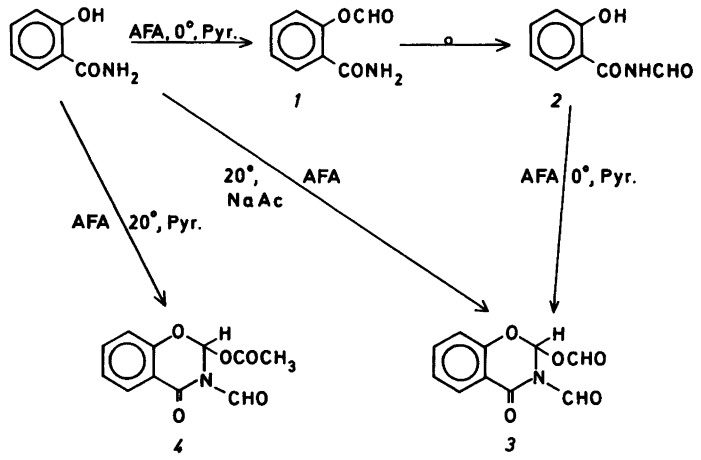
In connection with our interest in the reaction between salicylamide and triethyl orthoformate[1] we became aware of some interesting reactions between salicylamide and acetic formic anhydride, in which a 2,3-dihydro-1,3-benzoxazine-4-one structure was formed.

Formylation of salicylamide cannot be carried out by formic acid or ethyl formate, but acetic formic anhydride formylates salicylamide rapidly when a basic catalyst is used. If the formylation is carried out at 0 °C in chloroform solution with a few drops of pyridine as catalyst *O*-formylsalicylamide *1* is obtained in good yield (Scheme 1). Like the analogous *O*-acetylsalicylamide[2] *O*-formylsalicylamide rearranges readily to the *N*-formylsalicylamide. In DMSO-d_6 solution the rearrangement proceeds to 50 % within 40 min at room temperature. Reflux in toluene with a few drops of pyridine causes the *O*-formylsalicylamide to rearrange within a few min, which indicates that the formyl group migrates faster than the acetyl group.[2]

When the formylation reaction was carried out at room temperature with sodium acetate or very small amounts of pyridine as catalyst a compound with the composition corresponding to the introduction of three formyl groups into salicylamide was formed. The ^{1}H NMR spectrum of the compound showed three different C*H* signals at 6.95, 8.20 and 9.44 ppm and the ^{13}C NMR spectrum showed one significant diamagnetic shifted signal at 90.6 ppm, corresponding to an orthoester type carbon atom.

The structure of the compound must therefore be 2-formyloxy-3-formyl-2,3-dihydro-1,3-benzoxazin-4-one *3* (Scheme 1). Reaction between acetic formic anhydride and salicylamide carried out at room temperature in chloroform with greater amounts of pyridine as catalyst gave an analogous compound *4* with one formyl group and one acetyl group attached to the 2,3-dihydro-1,3-benzoxazin-4-one system. The IR spectra of *3* and *4* were similar to each other. The only differences were: the intensities of the absorp-



Scheme 1. (AFA=Acetic formic anhydride, NaAc=sodium acetate, Pyr.=pyridine).

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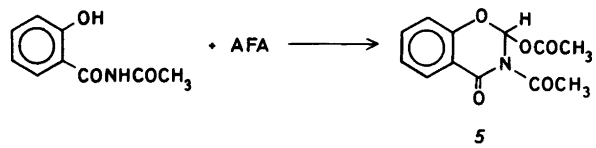

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Scheme 2.

tions, shifting of the 1750 cm^{-1} signal in *3* to 1770 cm^{-1} in *4* and some smaller pattern differences at lower wavelengths. From the ^1H NMR spectrum it could be seen that *4* was a *N*-formyl and not a *N*-acetyl compound because the formyl C*H* signal was found at 9.40 ppm. The C*H* signal for *O*-formyl is normally found at 8.15 ppm.

N-Acetylsalicylamide reacts with acetic formic anhydride to give compound *5* with two acetyl groups. At the same time *N,O*-diacetylsalicylamide is formed in almost the same yield (Scheme 2). From the ^1H NMR chemical shifts of the methyl groups it can be seen, that one of the acetyl groups in *5* is an *N*-acetyl group at 2.64 ppm and the other at 1.97 ppm an *O*-acetyl as in *4*, where the acetyl group was found at 2.01 ppm.

N-Formylsalicylamide treated in the same manner as *N*-acetylsalicylamide with acetic formic anhydride in chloroform solution with pyridine catalysis gave compound *3* and no acetyl group is introduced in the predominating reaction product.

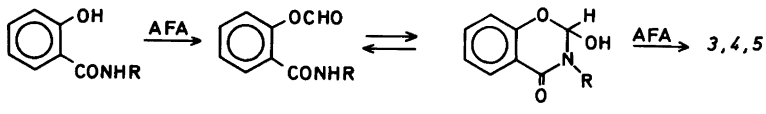
The *O*-formyl group seems essential for the reaction leading to dihydrobenzoxazine. Neither *O*-acetyl- nor *N,O*-diacetylsalicylamide or benzamide could react with acetic formic anhydride. This indicates that the free phenolic group is essential for initiation of the formylation with acetic formic anhydride. Since *N*-acetylsalicylamide reacts to dihydrobenzoxazine even at 0 °C, and the reaction does not stop at the *O*-formyl step as it does for unsubstituted salicylamide, the *N*-acetylation seems to accelerate the ring closure.

The mechanism for these reactions could therefore be explained by an initial *O*-formylation followed by an equilibrium between the *O*-formyl and the dihydrobenzoxazine structure. Dependent on temperature, catalyst and substitution of the salicylamide the next steps are formylation and/or acetylation (Scheme 3).

Experimental. The experimental equipment was reported earlier.[3] Melting points are uncorrected.

O-*Formylsalicylamide* 1. Salicylamide (0.05 mol) was dissolved in chloroform (50 ml), ten drops of pyridine were added, the solution cooled to 0 °C and acetic formic anhydride (0.15 mol) added during 30 min. After 1 h at 0 °C the unreacted salicylamide was filtered off and the filtrate cooled to −18 °C overnight. The *O*-formylsalicylamide was filtered off giving 53 % yield based on dissolved salicylamide. M.p. 97–99 °C. Anal. $C_8H_7NO_3$: C, H, N. ^1H NMR (DMSO-d_6): δ 6.90–8.03 (6 H, m), 8.45 (1 H, s). ^{13}C NMR (DMSO-d_6): δ 167.0, 160.6, 147.4, 131.5, 129.2, 126.2, 122.9. IR (KBr, cm^{-1}): 3320 (m), 3150 (m), 1730 (s), 1720 (s), 1660 (s), 1620 (s), 1400 (m), 1190 (s), 1110 (s). IR ($CHCl_3$, cm^{-1}): 3530 (w), 3400 (w), 1750 (m), 1675 (s).

2-*Formyloxy*-3-*formyl*-2,3-*dihydro*-1,3-*benzoxazin*-4-*one* 3 was prepared from salicylamide (0.05 mol), acetic formic anhydride (15 ml) and sodium acetate (5 g) in chloroform (65 ml). The mixture was stirred at room temperature for 3 h. The sodium acetate was filtered off and the filtrate washed with 5 ml ice-water. The chloroform-phase was dried over $MgSO_4$, evaporated to dryness and recrystallized from light petroleum giving *3* in 41 % yield. M.p. 86–88 °C. Anal. $C_{10}H_7NO_5$: C, H, N. ^1H NMR ($CDCl_3$): δ 6.95–8.20 (6 H, m), 9.44 (1 H, s). ^{13}C NMR ($CDCl_3$): δ 159.5, 159.1, 157.7, 153.9, 137.1, 128.6, 124.5, 117.8, 115.3, 90.6. IR ($CHCl_3$, cm^{-1}): 3020 (w), 1750 (s), 1725 (s), 1710 (s), 1610 (s), 1465 (s), 1390 (s), 1370 (m), 1320 (m), 1300 (s), 1260 (s), 1245 (s). *3* was also prepared from *N*-formylsalicylamide (0.02 mol) in chloroform (20 ml) with 10 drops of pyridine and acetic formic anhydride added in 15 min. The temperature was kept below 5 °C. After termination of the reaction all *N*-formylsalicylamide had dis-



Scheme 3.

solved and the reaction mixture was cooled to −18 °C giving 75 % yield of *3*.

2-Acetyloxy-3-formyl-2,3-dihydro-1,3-benzoxazin-4-one 4 was prepared from salicylamide (0.02 mol) and acetic formic anhydride (0.10 mol) in chloroform (20 ml) with 10 drops of pyridine. The mixture was stirred at room temperature. After 30 min all the salicylamide had reacted. The reaction mixture was evaporated to dryness and recrystallized from light petroleum-ethyl acetate. Yield 62 %, m.p. 115−117 °C. Anal. $C_{11}H_9NO_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.00 (3 H, s), 6.90−8.20 (5 H, m), 9.45 (1 H, s). ^{13}C NMR ($CDCl_3$): δ 168.0, 159.6, 154.1, 137.0, 128.6, 124.1, 117.8, 115.3, 91.0, 20.5. IR ($CHCl_3$, cm^{-1}): 3020 (w), 1770 (m), 1725 (s), 1710 (s), 1610 (m), 1465 (s), 1390 (m), 1370 (m), 1325 (m), 1305 (m), 1260 (m), 1250 (m).

2-Acetyloxy-3-acetyl-2,3-dihydro-1,3-benzoxazin-4-one 5 was prepared from *N*-acetylsalicylamide (0.02 mol) in chloroform (30 ml) with 10 drops of pyridine. Acetic formic anhydride (0.06 mol) was added at 0 °C in 30 min. After 1 h the reaction mixture was cooled to −18 °C and the precipitate recrystallized from light petroleum-ethyl acetate giving a yield of 37 % of *5*. M.p. 110−115 °C. Anal. $C_{12}H_{11}NO_5$: C, H, N. ^{1}H NMR ($CDCl_3$): δ 1.97 (3 H, s), 2.64 (3 H, s), 6.95−8.20 (5 H, m). ^{13}C NMR ($CDCl_3$): δ 171.1, 167.9, 159.9, 153.9, 136.3, 128.7, 123.7, 117.4, 116.3, 92.9, 26.9, 20.5. IR ($CHCl_3$, cm^{-1}): 3010 (w), 1760 (s), 1720 (s), 1610 (s), 1460 (s), 1380 (m), 1365 (s), 1320 (m), 1305 (m).

1. Treppendahl, S. and Jakobsen, P. *Acta Chem. Scand. B 35* (1981) 465.
2. Gordon, A. J. *Tetrahedron 23* (1967) 863.
3. Jakobsen, P. and Treppendahl, S. *Tetrahedron 38* (1982) 369.

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