HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

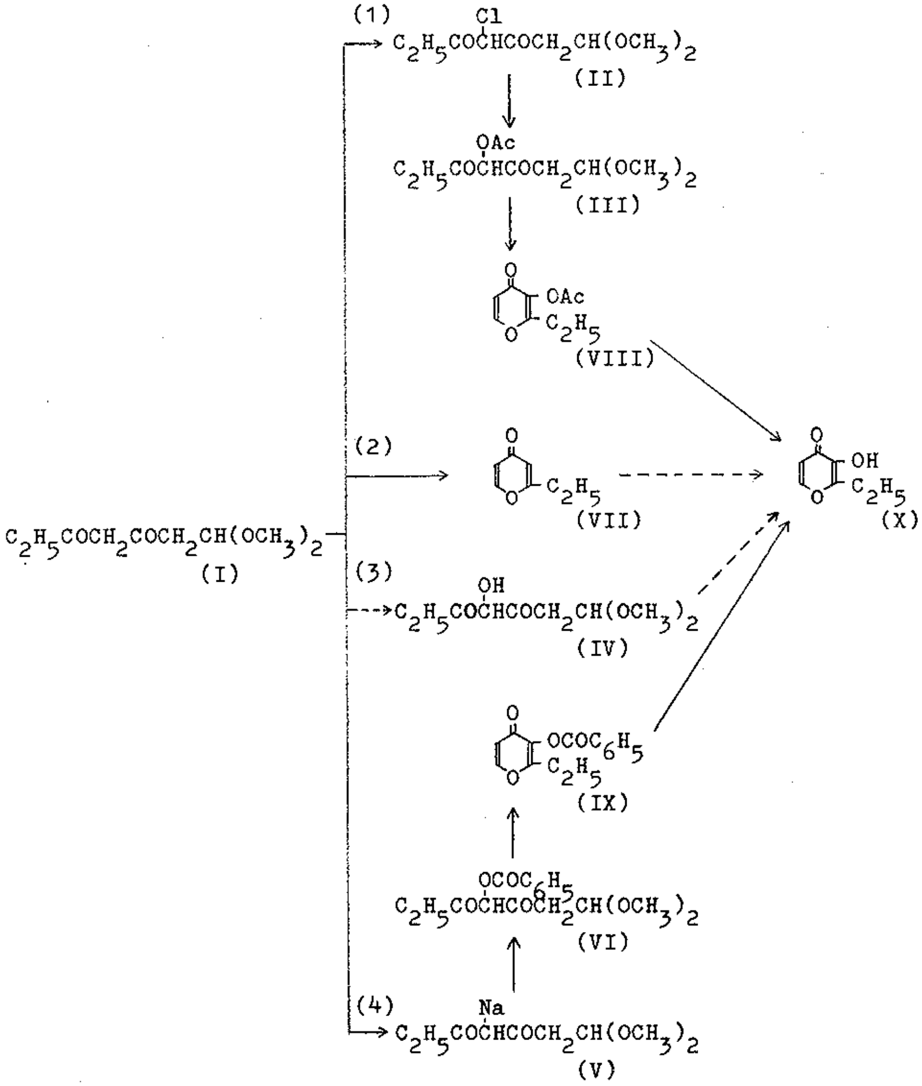
SOME ATTEMPTS TO INTRODUCE HYDROXYL GROUP INTO 2-ALKYL-4H-PYRAN-4-ONE

Ryoshu Suzuki, Takashi Hiramoto, and Itaru Takasu

Arai R&D Center / Central Research Laboratory
230 Oaza Arai, Arai-shi, Niigata-ken, 944

On the total synthesis of 2-alkyl-3-hydroxy-4-pyrone, the so-called Daicel Process consisting of four steps comprising 1) insertion of ketene into orthoformic ester, 2) Claisen condensation of the formed mono-inserted ester with methyl ketone, 3) acyloxylation toward active methylene in the formed beta-diketone, and 4) cyclizing condensation of the mono-acyloxylated beta-diketone and hydrolysis of the acyloxy group to hydroxy group had already been established.[1] Acyloxylating agent in the third step was found to be valid if it was lead tetraacetate or an aryl-iodoso-diacylate, but there were some problems by the waste disposal.

Here, four attempts were made to introduce a hydroxyl group into 2-ethyl-4-pyrone in place of the above third and fourth steps. These intentions are described by the following pathways:



(1) A method via chlorinated I

In a typical experiment, equimolar amount of SO_2Cl_2 diluted with CCl_4 was added into a mixture of I and CCl_4 and the reaction was completed. The solvent was then removed, the product was separated by extracting with ether and distilling the extract. GC analysis of this product showed that the yield of II was 21% and that of 2-ethyl-4-

pyrone was 40%.

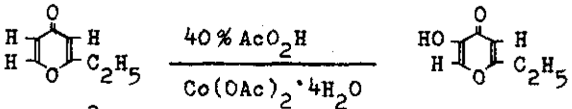
Generally the product consisted of many components and contained 15-20% chlorine (16%: theoretical). There being contained 30-50% unchlorinated product, it is thought for the rest to consist of highly chlorinated products in a fairly large amount. In order to ascertain the formation of II, a concentrated chlorination product containing about 50% II was reacted with KOAc at the boiling temperature of AcOH. Results showed that the yield of X attained to about 9% by means of colorimetric determination.

(2) A method via VII

Starting material I is readily cyclized by treating with a strong acid and/or by heating to convert into VII (in 97% yield). For the purpose of preparing X by the oxidation of VII, VII(0.01 mol), AcOH, and oxidizing agent(s) selected from the combinations of one of 60% H_2O_2(0.012 mol), BPO(0.010 mol), and 40% AcO_2H(0.007 mol) with $Co(OAc)_2 \cdot 4H_2O$(0.04 mmol) or none were reacted at fixed temperatures (50° and 120°C) for 2 h and then subjected to evaporation under reduced pressure and extraction with $CHCl_3$.

To confirm if the positive color test in a AcO_2H-$Co(OAc)_2 \cdot 4H_2O$-120°C run resulted from the formation of X, a ten-times scale experiment was carried out and the $CHCl_3$-extract was distilled to get a white crystalline product (a) through purifying the distillate. The product (a) possessed an intense caramel-like odour and a mp of 101°C higher than that of X as much as nearly 10°C.

Though the product (a) resembles X in IR and NMR spectra, the chemical shifts (in δ ppm) of 6.50 and 8.05 in (a) indicate apparently no mutual coupling, while 6.41 and 7.78 in X have each other a coupling constant equal to 6 Hz. Accordingly it is concluded that (a) is of an allomaltol-type structure in which a H-atom in 5-position of VII is replaced by a hydroxyl group.



L. C. Dorman[2] reported that among the coupling constants between ring protons of 2-methyl-4-pyrone the coupling constant between 3- and 6-position is of the smallest value: $J_{3,6} \leqq 0.6$ Hz, whereas $J_{3,5} = 2.5$ Hz and $J_{5,6} = 5.7$ Hz.

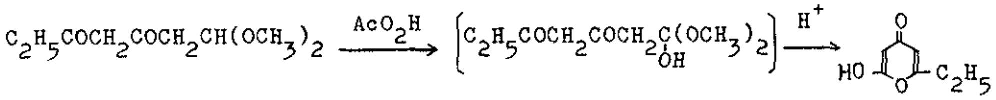
This information as well as the fact that allomaltol is known to be the only assigned product when 2-methyl-4-pyrone is reacted with AcO_2H support the above conclusion.

(3) A method by direct oxidation of I by the use of AcO_2H or H_2O_2

P. Karrel et al.[3] accomplished the oxidation of beta-diketones by perbenzoic acid to the corresponding 2-hydroxy compound and also H. O. House et al.[4] or A. J. Hubert et al.[5] conducted the similar experiments for beta-keto esters.

To examine the applicability of such a principle for the synthesis of X, direct oxidation of I was carried out. A mixture of 40% aqueous AcO_2H(0.1 mol) and AcOH was added slowly to a solution of I(0.1 mol) in AcOH at 100°C. The reaction mixture revealed positive colorization by $FeCl_3$-test. From the thickened and partly neutralized product, the organic ingredients were extracted with $CHCl_3$. A white crystalline product (b)(in 1.6% yield) of a mp of 85°C and sweet caramel-like odour was isolated by distilling the extract.

Though the product (b) also resembles X in IR and NMR spectra, the chemical shifts (in δ ppm) of 6.53 and 7.57 in (b) gave a coupling of $J \fallingdotseq 2$ Hz. Accordingly it is presumed that (b) is of a structure corresponding $J_{3,5} = 2.5$ Hz as previously stated. Thus the following scheme is accepted as the most plausible.

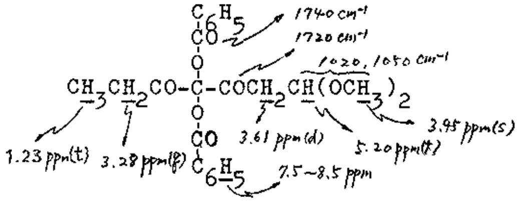


Colorimetric analysis indicated that the apparent yields of ones forming chelate with ferric ions were 15-16% in the case of AcO_2H oxidation and 7-10% in the case of H_2O_2 oxidation.

(4) An oxidation method by the use of benzoyl peroxide (BPO)

S. O. Lowesson et al.[6-9] presented that benzoyloxylation of an active methine group in a beta-dicarbonyl compound was attained in good yield by treating sodium salt of the beta-dicarbonyl compound with BPO. So, this method was applied to sodium salt of I.

Thus, into a stirred mixture of NaH(0.3 mol) and benzene was added dropwise a solution of I(0.3 mol) in benzene at 10-15°C. After the calculated amount of hydrogen evolved, precipitating sodium salt of I was collected in nearly quantitative yield. Next, into a stirred suspension of the salt V(0.05 mol) in benzene was slowly added a solution of BPO(0.05 mol) in benzene at 5-15°C. A greasy liquid product(16.6 g) was obtained by concentration from the reaction mixture washed with water. An aliquot of it was heated with 3.5 % HCl so as to give X and submitted to colorimetric analysis. Apparent conversion of V into X was estimated at 25 %. Another aliquot being dissolved in methanol at 50°C and cooled, a white crystalline product (c) melting at 108.7-109.4°C emerged. The IR and NMR spectra of (c) showed that this compound was assigned as follows:



$$CH_3CH_2CO-\underset{\underset{\underset{C_6H_5}{CO}}{O}}{\overset{\overset{\overset{C_6H_5}{CO}}{O}}{C}}-COCH_2CH(OCH_3)_2$$

Further experiments were carried out to find out the improved reaction conditions under which monobenzoyloxylation was effected and the best yield(46 %) of X was obtained when the reaction between sodium salt V(0.01 mol) and BPO carried out at 80°C (0.5+3 h) in the presence of CaH(0.4 g) and the mole ratio of BPO to V was adopted to be 0.9-1.0. Thus X was isolated as a crystalline product having a mp of 90.3-90.4°C through the treatment of the reaction mixture with H_2SO_4.

In conclusion, (1) in the case of chlorinating I polychlorination and cyclization reactions occurred besides monochlorination and desired product X could not be isolated; (2) although both peracetic acid and hydrogen peroxide were capable of oxidizing VII, the product in the former was not X, but was isomeric 2-ethyl-5-hydroxy-4-pyrone; (3) I was oxidized both by peracetic acid and by hydrogen peroxide similarly to (2), but the product was another isomer, 2-ethyl-6-hydroxy-4-pyrone;

(4) the introduction of benzoyloxy group into I was successful by reacting its sodium salt V with BPO, but the yield of X could not exceed 46%. Hereafter, more advanced methods should be sought.

References

(1) Japan.'71-17237; '76-21991; and others (to Daicel Ltd.)

(2) L. C. Dorman, J. Org. Chem., 32, 4105 (1967)

(3) P. Karrel et al., Helv. Chim. Acta, 33, 1711 (1950)

(4) H. O. House and W. F. Gannon, J. Org. Chem., 23, 879 (1958)

(5) A. J. Hubert and P. S. Starcher, J. Chem. Soc., (C) 2500 (1968)

(6) E. H. Larsen and S.-O. Lawesson, Organic Syntheses, 45, 37 (1965)

(7) S.-O. Lawesson et al., Arkiv Kemi, 17, 441 (1961)

(8) S.-O. Lawesson and S. Grönwall, Acta Chem. Scand., 14, 1445 (1960)

(9) S.-O. Lawesson et al., Tetrahedron, 19, 1229 (1963)