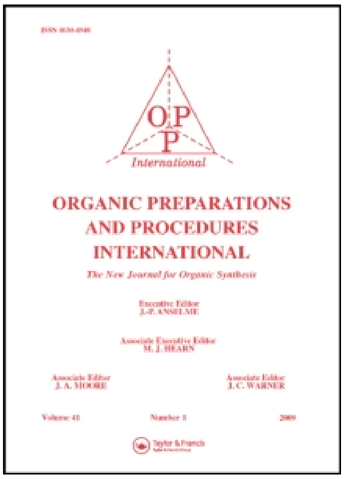

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# AN IMPROVED SYNTHESIS OF 2,4-DIOXO-3,8-DIOXABICYCLO[3.2.1]OCTANE

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# AN IMPROVED SYNTHESIS OF 2,4-DIOXO-3,8-DIOXABICYCLO[3.2.1]OCTANE

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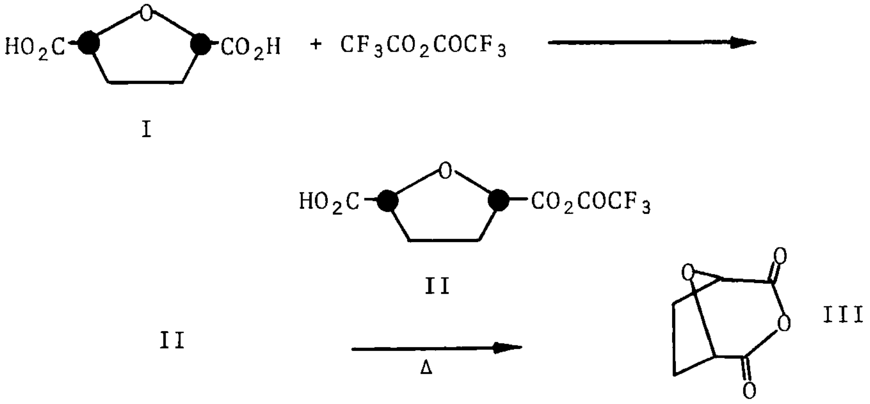
2,4-Dioxo-3,8-dioxabicyclo[3.2.1]octane, III, (tetrahydrofuran-cis-2,5-dicarboxylic acid anhydride) was first synthesized[1] in 1910. The procedure used involved refluxing tetrahydrofuran-cis-2,5-dicarboxylic acid, I, in acetyl chloride, producing III in about 50% yield, after correcting for recovered starting material. The actual conversion of I to III was 24% (2.8g of I yields 1.5g of I and 0.6g of III). We found these results to be reproducible in our laboratory.



Since then, several other methods have been developed for the synthesis of dicarboxylic anhydrides, including the use of carbodiimides[2], ynamines[3], acetic anhydride[4], $P_2O_5$[5] and reaction of carboxylic acids with acyl halides.[6]

Of particular interest to us, was the use of trifluoroacetic anhydride (TFAA) and pyridine[7], because we found it difficult to separate dicyclohexyl urea from the desired lactone in the synthesis of 2-oxo-3,8-dioxabicyclo[3.2.1]octane[9] from 5-hydroxymethyl-cis-2-tetrahydrofuroic acid using dicyclohexyl carbodiimide. Since the by-product from the TFAA method is a salt (pyridinium trifluoroacetate) it was thought that product purification would be less of a problem. However, this was not the case, because pyridinium trifluoroacetate is soluble in diethyl ether and III was not sufficiently soluble in solvents which do not dissolve pyridinium trifluoroacetate, to effect a complete separation.

The TFAA procedure calls for the addition of one mole of TFAA to one mole of dicarboxylic acid in ether. The resultant mono-mixed anhydride is treated with an equimolar amount of pyridine yielding the cyclic dicarboxylic anhydride and pyridinium trifluoroacetate. The anhydrides can be isolated in excellent yields (>90%) by addition of petroleum ether to precipitate the pyridinium trifluoroacetate (leaving the desired anhydride in solution) filtration and subsequent evaporation of the solvent. An alternative synthetic method, which was reported to give less satisfactory yields and purity, was to effect cyclization by heating the mixed anhydride in vacuo at 75°.

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When the above pyridine method was attempted for the synthesis of III we were unable to completely separate pyridinium trifluoroacetate from the desired anhydride, III because of their very similar solubility properties. However, we found that when the mixed anhydride II, was heated _in vacuo_ at 67° in a sublimator, excellent yields (>90%, corrected) of III were obtained as a white solid which collected on the cold finger. Thus, it should be noted that despite the previous caveat,[7] the thermolysis of the mixed anhydride of trifluoroacetic anhydride and dicarboxylic acids may, in certain cases, represent a highly satisfactory synthetic method.

The hydrolysis of III gave I in 96% yield.

## EXPERIMENTAL

_Synthesis of III_. - I, 5.0g (0.031 mole) was placed in a dry, 250ml, round bottom flask. Dry ether (NaH)(100ml) was added and the system was stirred for 20 min. Trifluoroacetic anhydride, 5ml (7.45g, 0.035 mole, Aldrich Chemical Company), was injected and the system was stirred for 1 hr. The resulting cloudy white solution was concentrated (rotary evaporator) to a white solid (II). IR 3500, 3000 (broad -OH), 1800 ($-CO_2CO-$), 1730 ($-CO_2-$), 1450, 1360, 1240, 1130, 990, 940, 870, 810, 730 $cm^{-1}$.

II was placed in a sublimation apparatus and heated for 6 hr at 67° (oil bath temperature) 0.1 mm Hg, yielding a white solid, IV, 3.47g which was scraped from the cold finger and a solid residue, 0,88g, which did not sublime and was found to be tetrahydrofuran-_cis_-2,5-dicarboxylic acid, mp. 125-6° (lit[8] mp. 125-6°). The corrected yield for III is therefore 95%, mp. 134-135° (lit[1] 128-129°) I.R. 1800 ($-CO_2-$), 1440, 1400, 1240, 1120, 1060, 990, 950, 880, 810, 740 $cm^{-1}$, nmr ($CDCl_3$) $\delta=2.08$ (m 4H $-CH_2-$ ring), $\delta=4.6$ (m, 2H, $-\overset{|}{\underset{|}{C}}H$ ring).

Hydrolysis of III. - III, 0.5g (0.0035 mole) was dissolved in water (25ml) and stirred for 1 hr. The resulting acidic solution was concentrated (rotary evaporator) to a white solid 0.54g, 96% yield, mp. 125-126°.

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