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FRIEDEL-CRAFTS ACYLATION OF TROPONE-IRONTRICARBONYL. SYNTHESIS OF β-THUJAPLICIN AND β-DOLABRIN.

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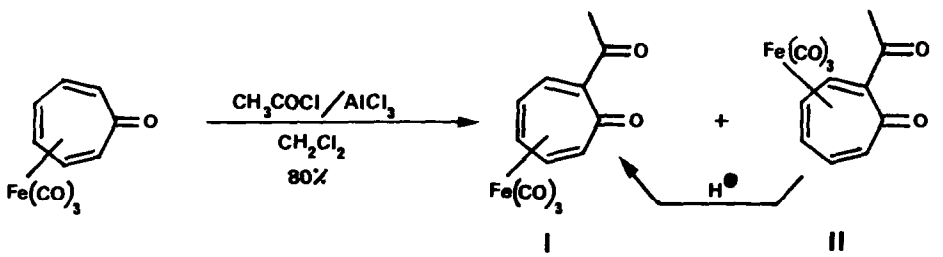
The natural tropolone β-thujaplicin IX has rather a simple structure ; In spite of this only a small number of unselective syntheses with poor yields are known (1), and of these, interestingly, no one starts from tropone itself (2).

Tropone is however an easily available material (3) whose direct isopropylation by means of 2-diazopropane similarly to simple α,β-unsaturated ketones or lactones (4) would lead to a much more straightforward synthesis.

Tropones react, in fact, with diazoalcanes in the "wrong" cycloaddition sense, leading mainly to cyclooctatrienones or their bicyclic valence tautomers by spontaneous decomposition of the intermediate Δ^1-pyrazolines (5). Complexation of tropone with iron tricarbonyl (6) is not sufficient to inverse the addition sense and hence give the isopropylation reaction (7). Therefore we tried to take advantage of the reactivity modification due to complexation, to introduce via Friedel-Crafts acylation a directing substituent, and thus achieve the "good" cycloaddition. Tropone and tropolones are known not to undergo the Friedel-Crafts substitution reaction (8). The tropone-irontricarbonyl complex, on the other hand, would be expected to undergo Friedel-Crafts acylation at carbon atom 2 at least considering the easy protonation at this position (9).

Tropone-irontricarbonyl, obtained here in 85% yield by irradiation of tropone with iron pentacarbonyl in toluene, reacts with a twofold excess of acetyl chloride and aluminium chloride in CH_2Cl_2 at room temperature to give a mixture of the tautomeric acetyltropone complexes I and II (~4/1) with an overall yield of 80% :



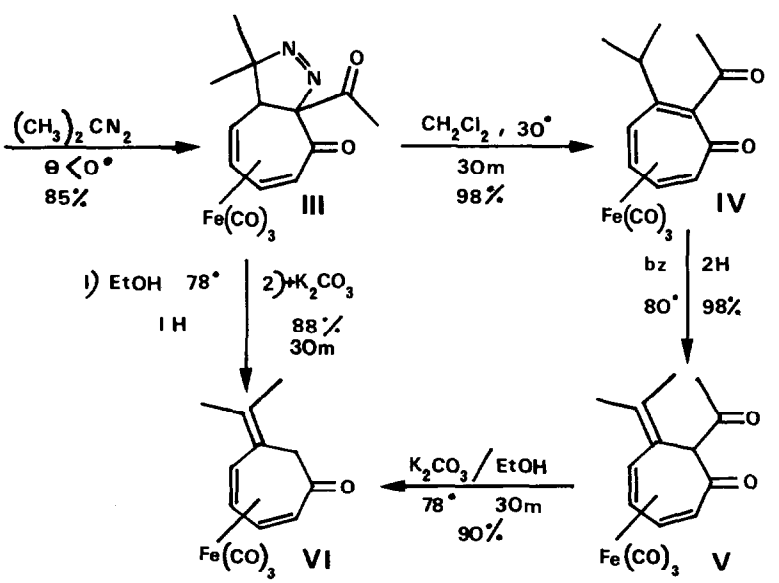
I II

I : purple crystals F = 70°C IR : 2080, 2000-2015, 1685, 1635 and 1585 cm^{-1}
NMR : 2,22ppm (3H,s) ; 3,21ppm (1H,d,8Hz) ; 7,48ppm (1H,d,8Hz) ; other H : 2,74ppm (1H,m) and 6,28-6,59ppm (2H,m).

II : red crystals F = 102°C IR : 2080, 2000-2015, 1690, 1635 and 1615 cm^{-1}
NMR : 2,34ppm (3H,s) ; 5,28ppm (1H,d,10Hz) ; 6,95ppm (1H,m) other H : 2,98ppm (1H,m), 6,38ppm (1H,dd) and 6,83ppm (1H,dd).

From the mixture of the interconverting complexes I and II one can obtain quantitavely the compound I by dissolution of the mixture in $HFSO_3$ followed by water treatment, neutralization and CH_2Cl_2 extraction. Compound II can be obtained by cooling a CH_2Cl_2/Ether solution of the mixture to - 78°C where it crystallises first, displacing the equilibrium entirely in its favor. Both complexes are stable in the solid state and no interconversion is then observed after longer periods at 0°C.

The complex I reacts readily even below 0°C with an excess of 2-diazopropane in ether. Cooling the solution to - 78°C yields crystals of the now reversed 1,3-cycloaddition product, pyrazoline III (85%) which loses nitrogen almost instantaneously at 85°C (10). Heating of a solution of III in CH_2Cl_2 at 30°C leads actually to the wanted isopropyl structure IV, isolated in 98% yield. This troponic complex is itself thermolabile and is almost quantitatively converted to the partly deconjugated complex V by heating of its benzenic solution at 80°C for 2 hours. This allows as a next step a smooth β-diketone alkaline splitting which proceeds rapidly in a refluxing ethanolic K_2CO_3 solution (Compound VI, 90%) :



III : yellow crystals F ~ 85°C (dec)
NMR (-30°C) CH_3 : 0,93ppm (3H,s) ; 1,82ppm (3H,s) and 2,21ppm (3H,s)
pyrazoline H : 3,60ppm (d,5Hz)

IV : red-orange crystals IR : ν(C=O) 1700 and 1610 cm^{-1}
NMR CH_3 : 2,18ppm (3H,s) ; 0,98ppm (3H,d,7Hz) and 1,18ppm (3H,d,7Hz)
isopropyl H : 2,48ppm (seven lines, 7Hz).

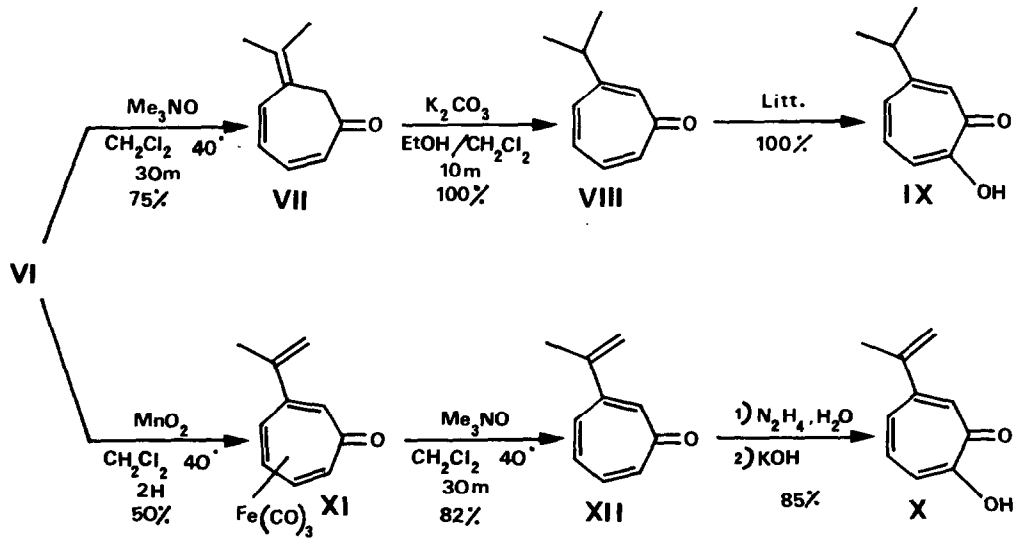
V : orange crystals F = 126°C IR : ν(C=O) 1720 and 1655 cm^{-1}
NMR CH_3 : 1,76ppm (3H,s) ; 1,91ppm (3H,s) and 2,04ppm (3H,s)
α-diketonic H (in C_6D_6) : 4,10ppm (s).

VI : yellow-orange crystals F = 85°C IR : ν(C=O) 1665 cm^{-1}
NMR CH_3 : 1,73ppm (3H,s) and 1,84ppm (3H,s)
CH_2 : 2,44 and 3,06ppm (AB 12Hz).

In a one-pot reaction it is thus easy to transform the complexed pyrazoline III into the trienone complex VI in nearly 90% overall yield with only one simple purification process (Filtration on SiO_2, elution hexane : ether).

From this stage on, the β-thujaplicin synthesis is achieved by decomplexing VI with Me_3NO in refluxing CH_2Cl_2 (Trienone VII, 75%) followed by base conjugation (100%), the conversion of the obtained β-isopropyltropone VIII to the corresponding tropolone IX being itself quantitative (1 f).

The more unsaturated natural tropolone β-dolabrin X, whose previous syntheses can hardly be considered to have a preparative value (11 a-c) is also readily available from the complex VI. Dehydrogenation with an excess of MnO_2 (12) in refluxed CH_2Cl_2 leads to β-isopropenyltropone-irontricarbonyl (XI, 50%) which in turn is decomplexed to the β-isopropenyltropone XII (82%) whose reaction with hydrazine followed by base treatment gives X (F=56°C, 85%):



VII : pale yellow oil IR : ν(C=O) 1660 cm^{-1} ν(C=C) 1630 and 1555 cm^{-1}
NMR CH_3 : 1,86ppm (3H,s) and 1,92ppm (3H,s) ; CH_2 : 3,39ppm (2H,s).

VIII : pale yellow oil IR : 1638 and 1570 cm^{-1} (tropone)
NMR Isopropyl group : 1,22ppm (6H,d,6,5Hz) ; 2,75ppm (1H, seven lines 6,5Hz)
other H : 6,83-7,12ppm (5H,m).

X : spectroscopical data identical with those of β-dolabrin (11a, 13).

XI : yellow-orange crystals F = 101°C IR : ν(C=O) 1615 cm^{-1}
NMR CH_3 : 1,87ppm (3H,s) ; CH_2 : 5,17ppm (1H,s) and 5,19ppm (1H,s)
α-ketonic vinylic H : 5,29ppm (s).

XII : pale yellow oil IR : 1640 and 1570 cm^{-1} (~tropone)
NMR CH_3 : 2,10ppm (3H,broad s)
CH_2 : 5,28 (1H, broad s) and 5,33ppm (1H, broad s); other H : 6,80-7,50ppm (5H,m)

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REFERENCES AND NOTES

All compounds gave satisfactory elemental analyses. Infrared spectra (IR) were obtained from samples as $CHCl_3$ solutions. NMR spectra, reported in δ units were recorded in $CDCl_3$ unless otherwise indicated using TMS as internal standard.

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2) Cf the statement of Noyori et al : No method has been known for the direct introduction of an alkyl group at C-3 position of troponoid skeleton (footnote 11 of reference 1e.).

3) One step from the commercial cycloheptatriene in 25% yield : P.RADLICK J.Org.Chem. 29, 960 (1964)
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6) The very weak ketonic character of tropone is enhanced in the complexed form where therefore a normal enone reactivity could be expected :
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7) This reaction leads in fact to a new homotropone synthesis :
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10) The complex II reacts with its free double bond with 2-diazopropane to give an inversed Δ^1-pyrazoline (90%). The latter leads by heating (2H, 80°C) only to a homotropone complex (90%). The reaction pathway followed by II is thus very similar to that of complex I itself (7).

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